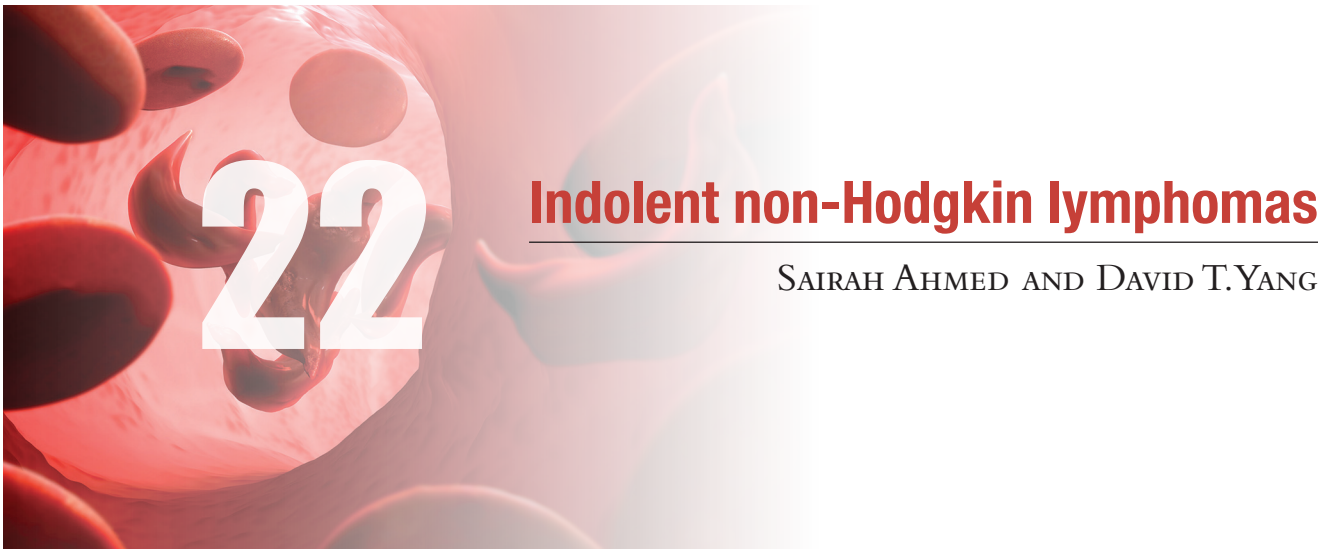

22 Indolent non-Hodgkin lymphomas

Sairah Ahmed and David T. Yang

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Overview of lymphocyte development and classification of lymphoid malignancies

The lymphoid system forms the backbone of the human immune system, contributing to both the innate (nonspecific) immune response through natural killer (NK) cells and the adaptive (specific) immune response through B and T cells. Non-Hodgkin lymphomas are malignancies that arise from these cells, generally grouped as B-cell lymphomas and T-cell lymphomas. Knowledge of B- and T-cell development is important in understanding the biology and, in turn, in providing insight into the behavior of the numerous subtypes of these lymphomas that are derived from their normal B- and T-cell counterparts.

B-cell development and the biology of B-cell lymphomas

Common lymphoid progenitors in the bone marrow derived from hematopoietic stem cells are the source of B and T cells. Unlike T cells, full B-cell maturation occurs in the bone marrow and begins with recombination of the *V*, *D*, and *J* gene segments of the immunoglobulin heavy chain (IgH) followed by the light-chain genes in order to generate a functional immunoglobulin that is expressed on the cell surface as B-cell receptor (BCR). The survival and maturation of B cells in the bone marrow, as well as the differentiation of mature B cells that have exited the bone marrow, are dependent on operative BCR signaling. Importantly, BCR signaling has also been found to be necessary for lymphoma development and evolution with many mature B-cell malignancies showing sensitivity to kinase inhibitors which disrupt BCR signaling.

Collectively, the primary function of B cells is to generate a vast diversity of immunoglobulins. Generating this diversity begins with the combinatorial diversity produced from random *V*, *D*, and *J* rearrangements. Combinatorial diversity is amplified by junctional diversity produced by the action of terminal deoxynucleotidyl transferase (TdT) where nucleotides are randomly added or deleted at the sites of *V*, *D*, and *J* fusion. Successful rearrangement of the heavy and light immunoglobulin chains (κ or λ) results in expression of functional IgM and IgD on the surface of mature B cells before they exit the marrow. These mature, but antigen-naïve, B cells then gain additional diversity when exposed to antigens in the germinal centers of secondary lymphoid organs, such as lymph nodes, mucosa-associated lymphoid tissue, or the spleen. Here, somatic hypermutation occurs in

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Off-label drug use: Lenalidomide in follicular lymphoma; rituximab in hairy cell leukemia; bendamustine, brentuximab vedotin, gemcitabine, ibrutinib, and lenalidomide in DLBCL; ibrutinib, and lenalidomide in primary central nervous system lymphoma; alemtuzumab, gemcitabine, lenalidomide, and liposomal doxorubicin in PTCL; mogamulizumab in Adult T-cell leukemia/lymphoma.

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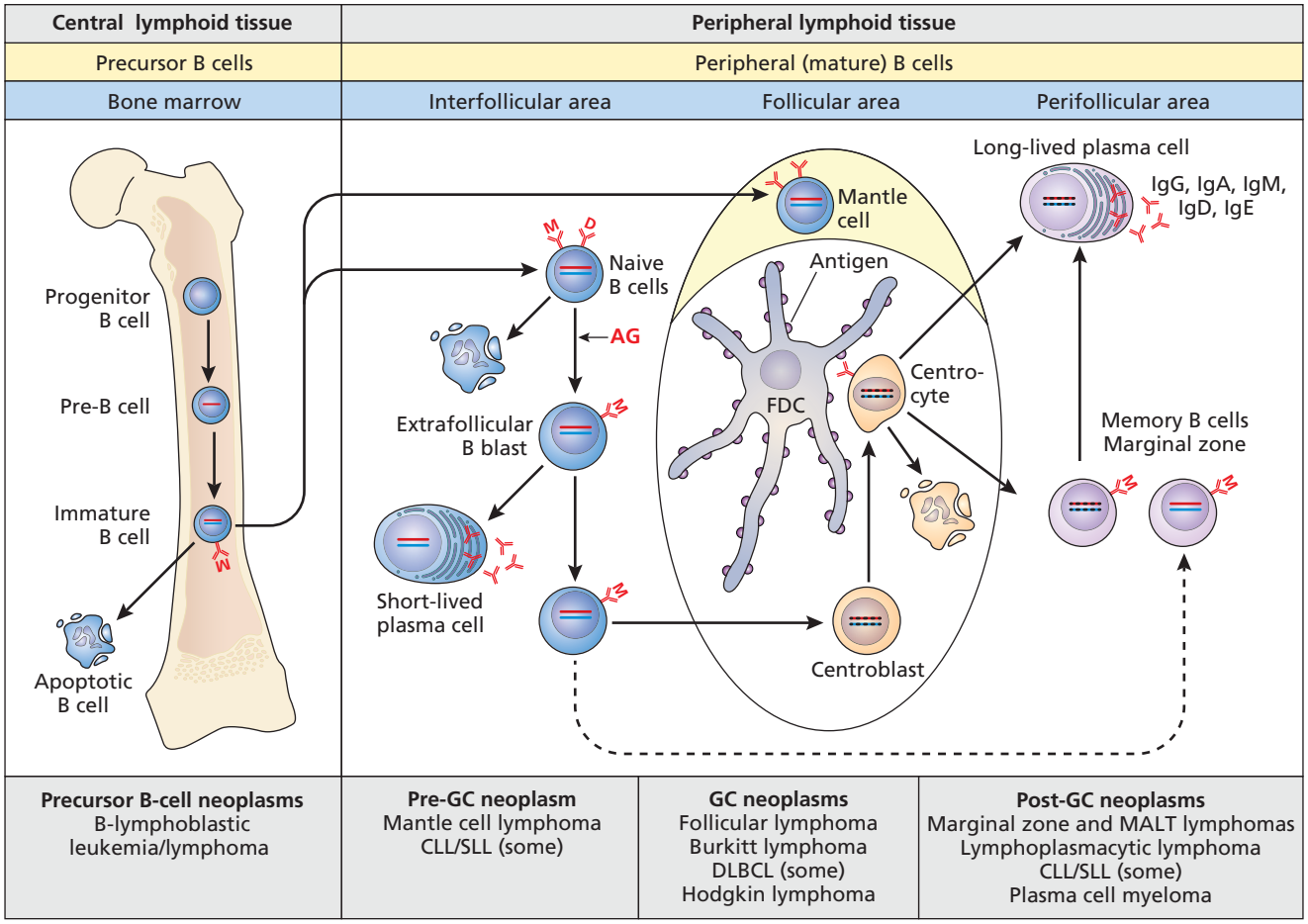

Figure 22-1 Schematic representation of B-cell differentiation (WHO 2017). AG, antigen; FDC, follicular dendritic cell. Reproduced with permission from Harald Stein.

the V genes of the heavy and light chains, fine-tuning their affinity to their cognate antigens. B cells expressing immunoglobulin with just the right amount of antigen affinity, differentiate to memory B cells and plasma cells while all the others undergo apoptosis. Finally, class switching occurs in the germinal center and involves changing the heavy chain that is expressed to produce IgG, IgA, or IgE.

The classification of B-cell lymphomas is based, in part, on the resemblance of a given lymphoma subtype to a particular stage in B-cell development and differentiation which reflects their origin and informs their biology (Figure 22-1). Distinct stages of B-cell development and differentiation are characterized by cytologic features, expression patterns of differentiation markers, and the BCR. These characteristics form the basis of pathologic diagnosis of lymphoid neoplasms. For example, B-lymphoblastic leukemia/lymphoma arises from an immature B-cell (Figure 22-1) and, accordingly, diagnosis requires the identification of immature B cells that have morphologic characteristics of blasts; coexpress B-cell markers, such as CD19, with markers of immaturity, such as TdT and CD10; and do not express BCRs on their surface. Likewise, follicular lymphoma (FL) arises from a germinal-center B cell (Figure 22-1) and has morphologic characteristics of nodular growth, resembling B-cell follicles, while expressing the germinal-center marker CD10 with surface IgM, IgD, IgG, or IgA.

The transformation of normal B cells into their malignant counterparts is closely linked to the essential role of B cells to generate immunological diversity, and thus, specific immunity. Conditions under which malignant transformation is fostered include viral infection, chronic bacterial infection, immune deficiency, autoimmune disease, and exposure to toxins (Table 22-1). Given the degree to which the immunoglobulin genes of B cells are subjected to DNA damage in the bone marrow and germinal centers, it is not surprising that reciprocal translocations, involving an immunoglobulin gene locus and

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Table 22-1 Risk factors in the development of non-Hodgkin lymphoma

Viral infection	EBV, HTLV-1, HHV-8, hepatitis C virus
Bacterial infection	*Helicobacter pylori*
	Chlamydophila psittaci
Impaired/altered immunity	Ataxia-telangiectasia
Congenital disorders	Wiskott-Aldrich syndrome
	X-linked lymphoproliferative syndrome
	Severe combined immunodeficiency
	Other immunodeficiency states
Acquired conditions of immunodeficiency	HIV infection
	Organ or stem cell transplantation
	Aging
	Chronic immunosuppressive medications
Autoimmune and rheumatologic disease	Rheumatoid arthritis
	Systemic lupus erythematosus
	Sjögren syndrome
	Celiac disease
Environmental or occupational	Herbicides
	Pesticides

a proto-oncogene, form the hallmark of many types of B-cell lymphoma (Table 22-2).

T-cell development and biology of the T-cell lymphomas

In contrast to B-cell development, T-cell progenitors derived from common lymphoid progenitors exit the marrow and develop in the thymus. Similar to B cells, each T cell recognizes a specific antigen, but through a T-cell receptor (TCR) rather than a BCR. Like BCRs, diversity of TCRs is generated through recombination of *V*, *D*, and *J* gene segments of the 4 TCR genes, *alpha* (α), *beta* (β), *gamma* (γ) and *delta* (δ). Mature T cells express αβ TCR or γδ TCRs. Of note, αβ TCRs can recognize antigens presented only in the context of a major histocompatibility complex (MHC) while γδ TCRs do not have this restriction. As such, NK cells and γδ T cells do not require antigen sensitization to become active and operate as part of our innate, rather than adaptive, immune system. Meanwhile, as developing T cells that express αβ TCR mature in the thymus, their αβ TCR is complexed with surface CD3 and CD4 or CD8, which identify helper and cytotoxic T-cell subsets, respectively (Figure 22-2).

Figure 22-2 Schematic representation of T-cell differentiation (WHO 2017). FDC, follicular dendritic cell; TFH, T-helper follicular cell. Reproduced with permission from Harald Stein.

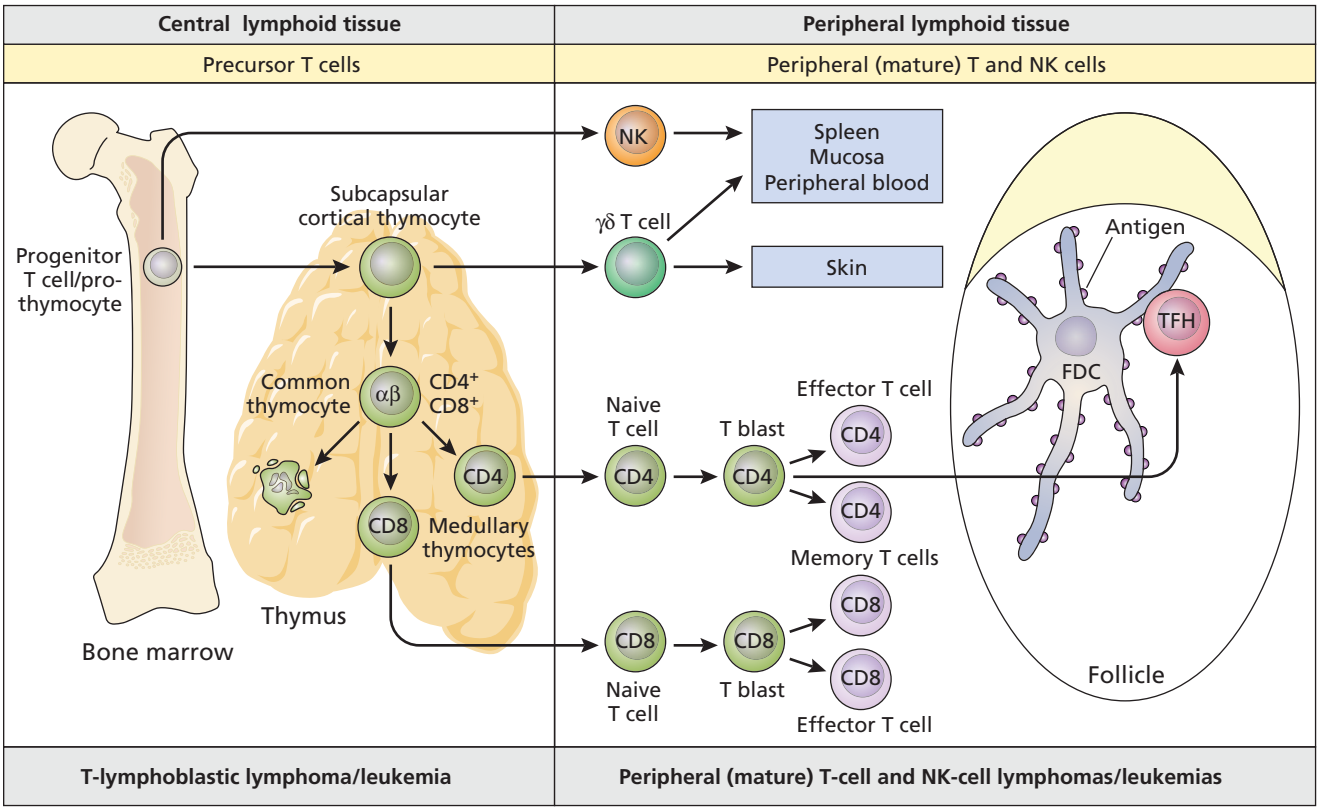

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Table 22-2 Phenotypic markers and common chromosomal translocations in selected non-Hodgkin lymphoma subtypes

NHL	sIg	CD5	CD10	CD20	Other	Cyclin D1	Cytogenetics	Oncogene	Function
CLL/SLL	Weak	+	–	Dim	$CD23^+$, $CD200^+$, FMC^-	–	No diagnostic abnormalities★	–	–
Follicular	++	–	+	+	$BCL2^+$, $BCL6^+$	–	t(14;18)	*BCL2*	Antiapoptosis
Mantle cell	++	+	–	+	Cyclin $D1^+$, $CD23^-$, $CD200^-$, FMC^+	+	t(11;14)	Cyclin D1	Cell cycle regulator
Marginal zone/ extranodal marginal zone lymphoma	+	–	–	+	–	–	t(11;18)	*AP12*-MALT	Resistance to *Helicobacter pylori* treatment
Lymphoplasmacytic lymphoma	++	–	–	+	$CD25^{+/-}$, $CD38^{+/-}$	–	–	*MYD88*	Proliferation
Hairy cell leukemia	++	–	–	+	$CD11c^+$, $CD25^+$, $CD103^+$, $BRAF^+$	Weak	–	*BRAF*	Proliferation
DLBCL	+	Rare	+/–	+	Variable	–	t(14;18), t(3;14), t(3;v)	*BCL2*	Antiapoptosis
							t(8;X)	*BCL6*	Transcription factor
								cMYC	Proliferation
								EZH2‡	Histone modifier
								MYD88§	Proliferation
PMBCL	–	–	–/+	+	$CD30^{+/-}$, $CD23^{+/-}$, $PD\text{-}L1^{+/-}$	–	t(16;X)†	*CIITA*	MHC class II transactivator
Burkitt lymphoma	+	–	+	+	$BCL6^+$, MYC^+, TdT^-, $BCL2^-$	–	t(8;14), t(2;8), t(8;22)	*cMYC*	Transcription factor
								TCF3/ID3	Transcription factor and its negative inhibitor
ALCL, ALK positive	–	–	–	–	$CD30^+$, $CD2^{+/-}$, $CD3^{-/+}$, ALK^+, EMA^+	–	t(2;5)	*ALK*	Tyrosine kinase
ALCL, ALK negative	–	–	–	–	$CD30^+$, $CD2^{+/-}$, $CD3^{-/+}$, ALK^-, EMA^-	–	t(6;7) (p25.3;q32.3)	*DUSP22*	Phosphatase

PMBCL, primary mediastinal large B-cell lymphoma; sIg, surface immunoglobulin.

★A number of prognostic cytogenetic abnormalities have been identified (see Chapter 24).

†A number of partner chromosomes described.

‡Exclusively in GCB-like DLBCL.

§Exclusively in ABC-like DLBCL.

The cell-of-origin approach that was so effective for categorizing B-cell lymphomas has been more difficult to apply to T-cell lymphomas due to a combination of factors including the complexity of mature T- and NK-cell lineages, with numerous functional subsets demonstrating marked phenotypic and morphologic diversity compounded by evidence of plasticity. In addition, with the noticeable exception of anaplastic lymphoma kinase-positive (ALK-positive) anaplastic large-cell lymphoma (ALCL), few recurrent cytogenetic abnormalities have been associated with mature T-cell lymphomas and, accordingly, contribute little to their categorization. Instead, clinical features and anatomic location of the disease have played major roles in defining many of the mature T- and NK-cell neoplasms included in the World Health Organization (WHO) classification, which can be grouped according to their presentation as predominantly leukemic, extranodal, or nodal disease (Table 22-3).

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Table 22-3 2016 World Health Organization classification of B-cell and T-cell neoplasms

B-cell neoplasms	T-cell neoplasms
Precursor B-cell neoplasms*	**Precursor T-cell neoplasms***
B-lymphoblastic leukemia/lymphoma NOS	T-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities	
Mature B-cell neoplasms	**Mature T-cell neoplasms**
Diffuse large B-cell lymphoma: variants, subgroups, and subtypes/entities	*Leukemic or disseminated*
Diffuse large B-cell lymphoma, NOS Germinal-center B-cell type Activated B-cell type	T-cell large granular lymphocytic leukemia† Chronic lymphoproliferative disorders of NK cells† T-cell prolymphocytic leukemia Aggressive NK-cell leukemia Adult T-cell leukemia/lymphoma Systemic EBV-positive T-cell lymphoproliferative disorders of childhood
Diffuse large B-cell lymphoma subtypes	*Extranodal*
T-cell/histiocyte-rich large B-cell lymphoma Primary DLBCL of the CNS Primary cutaneous DLBCL, leg type DLBCL associated with chronic inflammation HHV8-positive DLBCL, NOS EBV-positive DLBCL, NOS	Extranodal NK/T-cell lymphoma, nasal type Enteropathy-type T-cell lymphoma Monomorphic epitheliotropic intestinal T-cell lymphoma Hepatosplenic T-cell lymphoma Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract Breast implant–associated anaplastic large-cell lymphoma
Other lymphomas of large B cells	*Cutaneous*
Primary mediastinal large B-cell lymphoma Intravascular large B-cell lymphoma EBV-positive mucocutaneous ulcer Lymphomatoid granulomatosis ALK-positive large B-cell lymphoma Plasmablastic lymphoma Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman disease Primary effusion lymphoma	Mycosis fungoides† Sézary syndrome† Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorder† Primary cutaneous $CD4^+$ small/medium T-cell lymphoma† Primary cutaneous acral $CD8^+$ T-cell lymphoma† Primary cutaneous anaplastic large-cell lymphoma† Lymphomatoid papulosis Subcutaneous panniculitis-like T-cell lymphoma Primary cutaneous γδ T-cell lymphoma Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma Hydroa vacciniforme-like lymphoma
	Nodal
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma	Peripheral T-cell lymphoma, NOS Angioimmunoblastic T-cell lymphoma Follicular T-cell lymphoma Nodal peripheral T-cell lymphoma with TFH phenotype Anaplastic large-cell lymphoma, ALK positive Anaplastic large-cell lymphoma, ALK negative
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements	
High-grade B-cell lymphoma, NOS	
Burkitt lymphoma	
Burkitt-like lymphoma with 11q aberration	
Mantle cell lymphoma	
In situ mantle cell neoplasia	
Indolent lymphomas	
Follicular lymphoma In situ follicular neoplasia Duodenal-type follicular lymphoma Testicular follicular lymphoma Pediatric-type follicular lymphoma Large B-cell lymphoma with *IRF4* rearrangement	

Table continues on next page

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Table 22-3 2016 World Health Organization classification of B-cell and T-cell neoplasms *(continued)*

B-cell neoplasms	T-cell neoplasms
Primary cutaneous follicle-center lymphoma Extranodal marginal zone lymphoma of mucosa-associated lym phoid tissue Nodal marginal zone lymphoma Splenic marginal zone lymphoma Splenic B-cell lymphoma/leukemia, unclassifiable Lymphoplasmacytic lymphoma Heavy chain disease Plasma cell neoplasms CLL/SLL Monoclonal B-cell lymphocytosis B-cell prolymphocytic leukemia Hairy cell leukemia	

*All precursor lesions are considered aggressive.

†Indolent T-cell neoplasms, all other T-cell neoplasms are considered aggressive.

Diagnostic testing in lymphoproliferative disorders

Diagnosis of lymphoproliferative disorders requires some expertise and relies on a combination of morphologic findings (peripheral blood, bone marrow, or lymph node), immunophenotyping, cytogenetics, and molecular genetics.

Morphology

Well-stained peripheral blood and bone-marrow-aspirate smears provide excellent cytologic detail, facilitating evaluation of nuclear chromatin patterns and cytoplasmic coloration as well as revealing the presence of cytoplasmic inclusions and vacuoles in lymphoid cells. The degree of nuclear chromatin condensation is helpful in differentiating lymphoid blasts, which have finely granular or "open" chromatin, from mature lymphocytes, which have more opaque and condensed chromatin. Some lymphoid malignancies, such as chronic lymphocytic leukemia (CLL), have characteristic patterns of chromatin condensation, with CLL lymphocytes typically showing a "soccer ball" nuclear pattern. Likewise, Burkitt lymphoma (BL) cells can be recognized on smear preparations by their fine granular chromatin and strikingly blue, vacuolated cytoplasm.

Lymph-node biopsies and bone-marrow core biopsies lack the cytologic detail of smear preparations because tissue specimens must be fixed in formalin and dehydrated, a process that shrinks the cells and obscures cytologic detail. The benefit of tissue specimens is that they provide a glimpse of the underlying architecture, a critical component in differentiating benign from malignant lymphoid proliferations and in the classification of lymphoid malignancies. Lymphoid malignancies typically obliterate and "efface" underlying normal architectural features and the pattern of malignant growth, for example, nodular versus diffuse, guides subsequent classification. These patterns can be difficult to recognize in small biopsy specimens and, accordingly, needle-core biopsies of suspected lymphoid malignancies can be extremely challenging for pathologists to interpret.

Immunophenotyping

Immunophenotyping can be performed by flow cytometry on live cells from liquid specimens or disaggregated tissue. For fixed specimens, immunophenotyping is typically performed using 3,3′-diaminobenzidine-staining of tissue on glass slides. Immunophenotyping complements morphologic assessment by illuminating details of cell biology that would be otherwise imperceptible through the microscope. By determining cell lineage, maturation stage, and the presence of any aberrant antigen expression, immunophenotyping findings can be combined with morphologic findings to arrive at a diagnosis. For example, mantle cell lymphoma (MCL) is characterized by effacement of normal nodal architecture by small non-germinal center (CD10-negative) B cells (CD20 positive), with aberrant coexpression of CD5 (typically a T-cell marker, but expressed on a subset of B cells) and cyclin D1 (a protein that is not expressed in normal lymphocytes; its expression results from the translocation that underlies MCL). Other characteristic immunophenotypic profiles of lymphoid malignancies can be found in Table 22-2.

For B-cell malignancies, clonality can also be identified by light-chain restriction of the surface immunoglobulin. B cells normally express κ and λ light chains in a ratio of 2:1. A clonal expansion can be identified by a marked predominance of κ - or λ-expressing B cells that would not be expected in a reactive process. The immunophenotyping of T-cell neoplasms is less conclusive than for B-cell

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disorders because T cells lack the equivalent of light-chain restriction. Several findings can be suggestive of neoplasia, including expression of CD4 or CD8 on the majority of the T cells, lack of expression of CD4/CD8 on the majority of T cells, or coexpression of CD4 and CD8 on the majority of T cells. Often, however, molecular techniques to look at TCR gene rearrangements are necessary to differentiate reactive from clonal T-cell processes.

Molecular genetics and cytogenetics

Molecular genetic techniques can be helpful in assessing clonality when morphology and immunophenotyping are inconclusive. These techniques involve isolating the DNA from a sample and subjecting it to polymerase chain reaction (PCR) to detect rearrangements of immunoglobulin or TCR genes. The demonstration of a dominant rearrangement of the immunoglobulin or TCR genes is indicative of a clonal process.

Chromosomal translocations are common in lymphoproliferative disorders and may contribute to the transformation process or cellular proliferation (Table 22-2). Commercial probes are available for detection of most translocations by fluorescent in situ hybridization (FISH) and can be useful markers of malignancy and for identifying specific lymphoma subtypes. Use of microarray technology has defined gene-expression profiles of various lymphoid malignancies and compared them to normal lymphoid populations. This technique has been successfully applied to a number of B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL), FL, CLL, and MCL, to identify expression patterns that correlate with patient outcome. However, technical difficulty with assessing gene-expression profiles in the clinical laboratory, especially in formalin-fixed tissues, has hampered clinical application of these findings. Despite this, pathologists and oncologists have managed to apply the DLBCL gene-expression discoveries to the clinical realm by utilizing surrogate immunohistochemistry-based expression panels to differentiate the better-prognosis germinal-center B-cell-like DLBCL from the poor-prognosis activated B-cell-like DLBCL. More recently, next-generation sequencing (NGS) technology has been utilized to deeply interrogate the genomes of various lymphoid malignancies. While many such studies are still ongoing, landmark discoveries of single causative mutations of *BRAF* V600E in hairy cell leukemia (HCL) and *MYD88* L265P in Waldenström macroglobulinemia (WM) have thus far been reported (Table 22-2).

Assessment of lymphoma genetics via cell-free DNA (cfDNA) is an emerging analytic technique that has shown promise in assessing tumor kinetics, detecting occult disease, and assessing depth of response to therapy. This technique involves sequencing small fragments of cell-free DNA shed by apoptotic tumor cells into peripheral blood. Analysis of cfDNA ostensibly generates a more comprehensive assessment of tumor heterogeneity compared to tissue biopsy and facilitates serial monitoring of tumor genetics simply by phlebotomy. For patients with B-cell lymphoma, sequencing cell-free immunoglobulin receptor (VDJ) gene sequences by NGS can identify and quantify tumor-specific rearrangements thereby facilitating assessment of tumor kinetics during therapy as well as depth of response. The kinetics and clearance of tumor cfDNA in patients with DLBCL have been associated with prolonged progression-free survival. Likewise, assessment of lymphoma-relevant mutations other than immunoglobulin receptor genes by ultradeep sequencing of cfDNA can also be performed and clinical response in patients with DLBCL treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine, prednisone) found to be associated with clearance of cfDNA basal mutations in the peripheral blood.

Classification of non-Hodgkin lymphomas

The classification of lymphoproliferative disorders continues to evolve as our understanding of the biology of these diseases progresses. The current classification system used is the *World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues*, which was updated in 2017 (Table 22-3) and incorporates the explosion of new clinical, pathological, and genetic/molecular information that occurred since the previous 2008 publication. The B- and T-cell neoplasms are separated into precursor (lymphoblastic) neoplasms and mature B- or T-cell neoplasms. Overall, ~90% of all non-Hodgkin lymphomas (NHLs) in Western countries are of mature B-cell origin, with DLBCL and FL being the most common subtypes. In children, Hodgkin lymphoma (HL) is more predominant, and the aggressive NHLs of lymphoblastic lymphoma and BL are much more commonly encountered than are indolent neoplasms. The incidence of NHL is lower among Asian populations, in whom T-/NK-cell neoplasms are more frequent.

While the premise of the WHO classification is to separate lymphoid malignancies into distinct, nonoverlapping entities, it also recognizes that the biology of particular tumors crosses the boundaries between current categories. The classification of these gray-zone malignancies has been updated in the 2017 WHO monograph. "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma" remains unchanged, whereas "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt

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lymphoma" has been eliminated and replaced by "high-grade B-cell lymphoma, NOS (where NOS stands for 'not otherwise specified')" and "high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements." Common gene-expression and epigenetic profiles between primary mediastinal large B-cell lymphoma and classical Hodgkin lymphoma indicate a true biologic gray zone between these 2 entities exists. Likewise, certain cases of DLBCL have been found to have expression profiles of BL, although these cases differed clinically and genetically from classic BL and vice versa. Biologically, many of these cases may lie in the gray zone because they have rearrangements in both *cMYC* and *BCL2* or *BCL6* genes ("double-hit" lymphomas) and are more clinically aggressive than standard DLBCLs, hence their revised classification as "high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements." The remaining cases that exist in the boundary between BL and DLBCL without *MYC* and *BCL2* or *BCL6* rearrangements are now classified as "high-grade B-cell lymphoma, NOS."

For clinical purposes, the NHLs can be broadly separated into indolent or aggressive categories (Table 22-3). *Indolent lymphomas* generally are incurable with most standard therapeutic approaches and are typified by a chronic course with repeated relapses and progression with standard therapy. Some of these patients, however, survive many years with remarkably stable disease even in the absence of specific therapy. Median survival is measured in decades, and the majority of patients live a normal life expectancy compared to age-matched controls, thanks to the efficacy of modern therapy with the exception of those who are young at diagnosis and those who, following initial systemic treatment, progress rapidly or experience transformation into aggressive lymphomas (8%-10% risk at 5 years). Most, but not all, *aggressive lymphomas* are potentially curable with combination chemotherapy. Aggressive subtypes usually have a more acute presentation, often with B-symptoms (fever, night sweats, and weight loss), and a more rapid progression than the indolent entities. In the event of failure to achieve complete remission (CR) following treatment or with relapse after an initial therapeutic response, survival usually is measured in months rather than years. Some of these patients, however, are cured by second-line chemotherapy and stem cell transplantation approaches as described in the following chapter.

Epidemiology, pathogenesis, and molecular characterization

Data from cancer registries show that the incidence of NHL has been increasing steadily in North America and other industrial countries with a doubling of cases between 1970 and 1990 and stabilization thereafter. In 2021, there will be an estimated 81,560 new cases of NHL, representing 4% to 5% of all cancer diagnoses among men and women, and 20,720 deaths. The reasons for this increasing incidence are unknown but are the subject of ongoing epidemiologic investigations. Associations have been made with occupational exposure to certain pesticides and herbicides (Table 22-1). Agricultural workers with cutaneous exposure to these agents have a 2- to 6-fold increased incidence of NHL, possibly contributing to the relatively greater frequency of lymphoma in rural versus urban populations. Risk factors may differ between developing B- and T-cell lymphomas. A large epidemiologic study from the International Lymphoma Epidemiology Consortium (InterLymph) identified eczema, T-cell activating autoimmune diseases, a family history of myeloma, and occupation as a painter as increasing the risk for T-cell lymphoma. A history of B-cell-activating autoimmune disease and hepatitis C seropositivity were associated with increased risk for certain B-cell lymphomas.

Immunosuppression associated with HIV infection or iatrogenically induced immune suppression in the organ transplantation setting is associated with an increased incidence of aggressive B-cell lymphomas, likely due to dysregulated B-cell proliferation and susceptibility to viruses, such as Epstein-Barr virus (EBV) (Table 22-1). In children, the incidence of NHL is increased in several disorders that have immunodeficiency from primary immune disorders, including ataxia-telangiectasia, Wiskott-Aldrich syndrome, common variable or severe combined immunodeficiency, and X-linked lymphoproliferative disorder.

Infection with the bacterium *Helicobacter pylori* is strongly associated with gastric mucosa-associated lymphoid tissue (MALT) lymphoma (Table 22-1). Patients with MALT limited to the stomach often achieve CR after successful therapy to eradicate *H pylori*, indicating that the lymphoma remains dependent in part on continued antigenic drive from the microorganism. Associations have also been made between orbital infection by *Chlamydophila psittaci* and orbital adnexal MALT lymphoma, infection with *Campylobacter jejuni* and immunoproliferative small intestinal disease, and *Borrelia burgdorferi* or *Borrelia afzelii* and cutaneous MALT lymphoma. These intriguing associations need to be firmly established by additional investigation. Response to antimicrobial therapy among MALT lymphomas driven by infectious pathogens has been highly variable. The majority of gastric MALT lymphomas respond to *H pylori* directed antibiotic treatment, while response of ocular adnexal or cutaneous MALT lymphomas to *Chlamydophila*- or *Borrelia*-directed

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therapies, respectively, has been unsuccessful overall, with some geographic variability.

Certain viral infections have been linked with specific subtypes of NHL. EBV has a clear pathogenic role in endemic, as well as in some cases of sporadic, BL and in many cases of HIV-related aggressive B-cell lymphoma and discrete subtypes of B-cell and T-cell lymphomas. EBV-positive DLBCL NOS is thought to be associated with age-related immunosuppression. EBV is strongly associated with extranodal T-/NK-cell lymphoma, nasal type, which is seen most commonly in Asia and in Central and South America. EBV is also detected in 70% to 80% of cases of angioimmunoblastic T-cell lymphoma. The gammaherpesvirus human herpesvirus 8 (HHV-8, also called Kaposi sarcoma–associated herpesvirus), first described in Kaposi sarcoma but also associated with an unusual primary body cavity lymphoma (primary effusion lymphoma), is most commonly seen in patients with AIDS. HHV-8 also has been described in association with multicentric Castleman disease. The retrovirus human T-cell lymphotropic virus 1 (HTLV-1) is associated with adult T-cell leukemia/lymphoma endemic to Japan, central Africa, and the Caribbean. Chronic hepatitis C virus infection has been linked to the development of B-cell NHL, particularly marginal zone lymphoma and DLBCL, possibly via chronic BCR stimulation through direct binding of a viral envelope protein.

Specific chromosomal translocations are strongly associated with individual subtypes of B-cell NHL (Table 22-2). The majority of these arise early in B-cell differentiation, during the process of immunoglobulin gene rearrangement, when errant fusion of immunoglobulin promoter and enhancer elements with other genes leads to dysregulated oncogene expression. Careful study of such translocations has provided important insights into pathogenic mechanisms in lymphoma. The most frequent of these translocations are as follows: (1) t(14;18), with resultant overexpression of the antiapoptotic gene *BCL2*, which is present in ~85% of FLs; (2) t(11;14) with cyclin D1 overexpression, which is present in virtually all MCLs; and (3) t(8;14), t(2;8), and t(8;22) of BL, which fuse an immunoglobulin heavy- or light-chain gene promoter to the *cMYC* transcription factor. *BCL6*, a chromosome-3 transcription-factor gene capable of promiscuous rearrangement with multiple translocation partners, is most commonly identified in DLBCL. The t(2;5) (p23;q35) fuses the *ALK* gene with nucleophosmin and is found in a subset of ALCL. Several other translocation partners with the *ALK* gene also have been described in this disease. This translocation and *ALK* expression are associated with a more favorable prognosis in ALCL (see also the section "Indolent peripheral T-cell lymphomas" in this chapter). Among ALCL patients without an ALK rearrangement, DUSP22 translocations have been found in a subset of cases and predict a favorable prognosis.

Gene expression profiling has defined molecular signatures in lymphoma that have been utilized to identify prognostically significant disease subsets in DLBCL, FL, MCL, CLL, and T-cell ALCL as well as illuminating the existence of gray-zone lymphomas that lie between DLBCL and BL, as well as DLBCL and classical Hodgkin lymphoma. More recently, next-generation sequencing has provided some early insight into the mutational landscape of several lymphomas including the previously mentioned single causative mutations of *BRAF*V600E in HCL and *MYD88* L265P in Waldenström macroglobulinemia. Additionally, the mutational landscape of germinal-center B-cell (GCB)-like DLBCL has been found to be distinct from activated B-cell (ABC)-like DLBCL, with GCB-like DLBCL harboring activating *EZH2* mutations and ABC-like DLBCL harboring activating *MYD88* and *CD79B* mutations. These discoveries continue to refine lymphoma classification and elucidate novel therapeutic targets.

Staging and prognostic factors

Staging procedures generally include careful physical examination for lymphadenopathy and organomegaly; computed tomography (CT) scans of the neck, chest, abdomen, and pelvis; fluorodeoxyglucose positron emission tomography (FDG-PET) imaging; and may require bone marrow biopsy. CT or magnetic resonance imaging (MRI) of the brain and evaluation of the cerebrospinal fluid are not generally indicated for patients with indolent lymphoma unless there is clinical suspicion. PET imaging is preferred for staging FDG-avid nodal lymphomas, while CT alone is preferred for non-FDG-avid and variably FDG-avid histologies. In essence, all nodal lymphoma histologies are considered FDG-avid except lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia, mycosis fungoides (MF), and marginal zone lymphoma. However, PET imaging may still be helpful in these histologies to evaluate for transformation of disease. The Ann Arbor staging system, identifying patients as having stage I (localized) to stage IV (extensive extranodal) disease, originally was devised for use in HL but was later adopted for use in NHL. Patients are further stratified as to the absence (A) or presence (B) of systemic symptoms, namely, fevers, drenching night sweats, or unintentional weight loss of 10% or more within 6 months of diagnosis. Several limitations become apparent when the Ann Arbor classification is applied to NHL and, as a result, a revised staging system, called the Lugano classification, was proposed in 2014 (Table 22-4). Patients with Ann Arbor stage I or II

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Table 22-4 Lugano staging system for NHL

Stage		Involvement	Extranodal (E) status
Lugano	Ann Arbor		
Limited	I	One node or a group of adjacent nodes	Single extranodal lesion without nodal involvement
Limited	II	Two or more lymph node regions on the same side of the diaphragm	Stage II by nodal extent with limited contiguous extranodal extension
Advanced	III	Involvement of lymph node regions on both sides of the diaphragm, nodes above the diaphragm with or spleen involvement	Stage III by nodal extent with limited contiguous extranodal extension
Advanced	IV	Additional noncontiguous extralymphatic involvement	Not applicable

Table 22-5 The IPI in DLBCL in the rituximab era

Risk factors*	3-year PFS	3-year OS
0, 1	87%	91%
2	74%	81%
3	59%	65%
4, 5	56%	59%

*IPI risk factors are age ≥60 years, abnormal LDH, PS ≥2, stage III or IV, and >1 extranodal sites.

disease can be grouped and considered as having "limited-stage" disease whereas patients with Ann Arbor stage III or IV disease can be grouped and considered as having "advanced-stage" disease. Other recommendations from the Lugano classification include the following: (1) consider FDG-PET/CT as standard imaging for FDG-avid lymphomas but employ CT for non-FDG-avid histologies; (2) reserve the suffix A or B only for HL; (3) eliminate the X designation for bulky disease (because there is no universal definition for bulk) and replace it with a recording of the largest nodal diameter; and (4) eliminate the need for staging bone-marrow biopsies in aggressive NHL histologies if a PET-CT scan was used for staging.

Lymphoma staging has only limited prognostic usefulness. To more fully incorporate additional relevant prognostic features, models have been developed in multiple NHL subtypes, including DLBCL, FL, and MCL. The most widely used clinical prognostic model for stratifying patients with aggressive NHLs is the International Prognostic Index (IPI). The purpose was to identify pretreatment variables that predict relapse-free and overall survival (OS) in patients treated with doxorubicin-containing combination chemotherapy. The following 5 risk factors were found to be independently associated with clinical outcome and may be referred to by the mnemonic *APLES*: (1) age older than 60 years, (2) Eastern Cooperative Oncology Group (ECOG) performance status (PS) >1, (3) elevated serum lactate dehydrogenase (LDH), (4) number of extranodal sites of disease >1, and (5) stage III or IV. The IPI score is derived as a simple additive score from 0-5, has been widely adopted to estimate prognosis in patients with NHL, and is useful in some of the other lymphoma subtypes. Of note, these survival estimates were established before the use of rituximab for diffuse large B-cell lymphoma.

Limited studies support that the IPI is still prognostic in the rituximab-treatment era. A revised IPI (R-IPI), based on data from the British Columbia Cancer Agency, may define new risk groups in rituximab-treated patients: very good risk (0 risk factors, 4-year progression-free survival [PFS] 90%); good risk (1, 2 risk factors, 4-year PFS 70%); and poor risk (>2 risk factors, 4-year PFS 50%). The Deutsche Studiengruppe für Hochmaligne Non-Hodgkin-Lymphome (DSHNHL) group also evaluated the usefulness of the IPI in over 1000 patients enrolled on prospective clinical trials and found that IPI did effectively separate patients into the previously established risk categories with 3-year PFS ranging from 56% in the highest risk patients to 87% in the lowest risk (Table 22-5).

Although the IPI scoring system provides useful prognostic information, there is no definitive evidence that outcome is altered by using intensive regimens in high-risk patients. Numerous studies have been reported and others are still in progress that assess the utility of the IPI and "risk-adjusted" or "risk-adapted" therapeutic strategies. These include trials of high-dose therapy (HDT) and autologous stem cell transplantation for aggressive lymphoma patients with high IPI scores; however, such strategies currently are not routinely recommended because standard approaches are effective in the majority of patients, and the value of HDT has only been suggested in underpowered subset analyses of larger clinical trials showing no statistical benefit for this approach in the overall patient population (see the section "Diffuse large B-cell lymphoma" in the following chapter). The IPI is useful in comparing studies and also in the investigation of new prognostic factors to determine the independent effect on outcome.

The IPI score is predictive of survival in indolent lymphomas, namely, FL, although using the IPI, the majority of these patients fall into the low-risk or low-intermediate-risk categories. As such, a new index was developed specifically

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Table 22-6 The Follicular Lymphoma International Prognostic Index

Risk model and group	No. of factors	Distribution of cases (%)	5-year OS (%)	10-year OS (%)
FLIPI*				
Low	0-1	36	91	71
Intermediate	2	37	78	51
High	≥3	27	53	36

*FLIPI risk factors: No-LASH, number of nodal sites of disease >4, elevated LDH, age >60 years, stage III or IV disease, and hemoglobin ≤12 g/L.

Table 22-7 The Mantle Cell Lymphoma International Prognostic Index

Points	Age, years	ECOG PS	LDH/ULN	WBC, cells/mm^3
0	<50	0-1	≤0.67	<6700
1	50-59	—	0.67-0.99	6700-9999
2	60-69	2-4	1.00-1.49	10,000-14,999
3	≥70	—	≥1.50	≥15,000

MIPI risk factors are age, PS, LDH, WBC level.

Formula for MIPI: [0.03535 × age (years)] + 0.6978 (if ECOG >1) + [1.367 ×log10(LDH/ULN)] + [log10(WBC count)].

Simplified MIPI: low risk, 0-3 points; intermediate risk, 4-5 points; high risk, 6-11 points.

LDH, [lactate] dehydrogenase; ULN, upper limit of normal.

for FL, called the Follicular Lymphoma International Prognostic Index (FLIPI), in hopes of better stratifying patients (Table 22-6). This index can be remembered by the mnemonic No-LASH. The 5 clinical factors that are the strongest predictors of outcome in multivariate analysis were as follows: (1) number (no.) of nodal sites of disease (>4), (2) elevated LDH, (3) age older than 60 years, (4) stage III or IV disease, and (5) hemoglobin <12 g/dL. Compared with the IPI, the FLIPI provides a better distribution of patients across the risk categories of low risk (0 to 1 factor), intermediate risk (2 factors), or high risk (>2 factors). The 10-year OS rates were 71% (low risk), 51% (intermediate risk), and 36% (high risk), respectively (Table 22-6). Similarly, an international prognostic index for MCL (the Mantle Cell Lymphoma International Prognostic Index [MIPI]) also has been developed and incorporates age, PS, LDH, and white blood cell (WBC) level (Table 22-7).

Role of FDG-PET imaging

FDG-PET scanning is useful both for staging and for assessing response to lymphoma therapy and is generally recommended as part of routine staging and end-of-treatment response assessment in FDG-avid lymphomas. The 5-point scale (Deauville criteria [Table 22-8]) should be used for PET interpretation, and scores of 1 to 3 at completion of therapy

Table 22-8 Deauville 5-point scale for PET interpretation in lymphoma

Score	Visual description
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but less than liver
4	Update moderately higher than liver
5	Update markedly higher than liver

are considered consistent with complete remission, regardless of the size of any residual masses. Some studies indicate that interim PET scanning, performed mid-treatment, can identify patients at higher risk for treatment failure; however, it is unknown whether therapy should be altered based upon the results of a mid-treatment PET scan. False-positive results can occur in the setting of inflammation, granulomatous disease, and infection, and a biopsy should be performed in a PET-positive patient in remission by CT scan if further therapy is under consideration.

Patient management and follow-up

With over 60 lymphoma subtypes, detailed management guidelines for each subtype and disease stage are beyond the scope of this chapter. The reader is encouraged to refer to the National Comprehensive Cancer Network (NCCN) guidelines at http://www.nccn.org/, an outstanding resource for the treating clinician.

Patient surveillance following treatment of lymphoma should address both long-term complications of therapy and disease recurrence. Long-term effects of therapy depend on the type of treatment and whether radiotherapy (RT) was also administered. For example, radiotherapy to the head and neck region leads to decreased salivation with dental caries, and if the thyroid is included in the radiation field, a large proportion of patients eventually become hypothyroid. Women who have had mantle radiation should receive a mammogram beginning 10 years after radiation or at age 40 years, whichever comes first. In younger women, MRI breast imaging also can be considered, given the reduced sensitivity of mammography in this population.

Long-term survivors are at risk of second malignancies, which are dependent on the treatment administered. For example, radiated patients are at risk for carcinomas and sarcomas in the radiated field, while those who have had alkylating agents are at risk for therapy-related myelodysplastic syndrome or acute myeloid leukemia. Once primary therapy has been completed and remission is documented, patients typically are followed every 3 months for the first 2 years, then every 6 months until 5 years, and then annually thereafter.

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Most recurrences of aggressive lymphoma occur in the first 2 years after treatment, although late relapses beyond 5 years do occur in a minority of patients. Patients with indolent lymphoma have a lifelong risk of relapse and typically are seen every 3 months for the first 2 years and then every 6 to 12 months indefinitely. There is no evidence that routine CT or PET imaging affects outcome of patients, and newer guidelines recommend minimizing surveillance imaging in indolent lymphomas.

KEY POINTS

- NHLs are biologically and clinically heterogeneous; accurate diagnosis by a hematopathologist using the WHO classification is essential for optimal management.
- The majority of NHLs are of B-cell origin and are categorized broadly as indolent versus aggressive subtypes.
- The incidence of NHL in Western countries increased in recent decades, but is currently stable.
- Specific chromosomal translocations are associated with specific subtypes of lymphoma and are pathogenetically involved in malignant transformation and progression.
- The IPI score provides important prognostic information for outcome and survival in aggressive lymphomas. The FLIPI has been developed specifically for FL.

Indolent B-cell NHL

The indolent B-cell lymphomas include the histologies shown in Table 22-3, and the most commonly encountered subtype is FL, which accounts for 20% to 30% of all lymphomas. Other subtypes include marginal zone lymphomas (nodal, splenic, and extranodal [MALT] types) and lymphoplasmacytic lymphoma. This category also includes CLL/small lymphocytic lymphoma (SLL), which is discussed in Chapter 24.

CLINICAL CASE

A 53-year-old man is diagnosed with stage III FL after noticing a lump on his neck while shaving. A biopsy reveals a lymph node with enlarged, closely packed follicles with distorted architecture. Inside the follicles are small lymphocytes with irregular nuclei. The cells stain positive for CD20, CD10, and BCL2. The staging evaluation reveals widespread lymphadenopathy, involving 5 nodal groups, with the largest node measuring just over 3 cm. The hemoglobin and LDH are normal. He has no disease-related symptoms and his ECOG PS is 0. The FLIPI score is 2, and he has a low tumor burden by the Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria.

Follicular lymphoma

FL is the prototypical and most common indolent lymphoma, with about 15,000 new cases diagnosed each year in the United States. Although incurable, the prognosis is quite good and has substantially improved in the modern era with the majority of patients now predicted to have a normal life expectancy compared to age-matched controls.

FLs are derived from germinal-center B cells and are graded based on the number of centroblasts per high-power field: grade 1-2 (0-15), and grade 3 (>15). Grade 3 is further classified into grade 3A (centrocytes present) and grade 3B (solid sheets of centroblasts). Grade 1-2 constitutes the typical low-grade follicular lymphoma, while grade 3 FL is relatively uncommon (<20% of all FLs); the natural history of this entity is less clear but may behave more aggressively. Most contemporary clinical trials allow grade 3A to be included with grade 1-2 cases, whereas grade 3B is excluded and managed akin to DLBCL. Immunophenotypically, FL cells are $CD20^+$, $CD10^+$, $BCL6^+$, $BCL2^+$, and $CD5^-$. Up to 90% of cases have a t(14;18) with a higher frequency observed in grade 1-2 FLs.

The 2016 WHO classification has identified several variants of FL. These include in situ follicular neoplasia, duodenal-type follicular lymphoma, and testicular follicular lymphoma; alongside 3 separately classified indolent B-cell lymphomas of follicle-center origin, primary cutaneous follicle-center lymphoma, pediatric-type follicular lymphoma and large B-cell lymphoma with *IRF4* rearrangement. "In situ follicular neoplasia" replaced the previous diagnosis of "in situ follicular lymphoma," consistent with growing conservatism in diagnosis of lymphoid neoplasia with a low rate of progression. Both duodenal-type and testicular follicular lymphomas are localized, biologically distinct, extranodal variants of FL that have excellent long-term outcomes with watch-and-wait approaches after surgical excision.

Primary cutaneous follicular-center lymphoma should be distinguished from FL. It is derived from follicle-center cells and can have a follicular, follicular and diffuse, or diffuse growth pattern. Unlike nodal FL, the neoplastic cells are usually BCL-2 negative and typically occur as solitary or localized skin lesions on the scalp, forehead, or trunk; only 15% present with multifocal lesions. The clinical course is usually very indolent and can be managed with low-dose radiation and other site-directed approaches.

Likewise, pediatric-type follicular lymphoma and large B-cell lymphoma with *IRF4* rearrangement are distinguished from FL in the 2016 WHO. As the name suggests, pediatric-type FL typically occurs in children and young

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adults and is a nodal disease characterized by large expansile highly proliferative follicles comprised of blastoid cells that lack the typical t(14;18) translocation and are BCL-2 negative. Despite the aggressive cytologic features, the prognosis is excellent with nearly all cases presenting with localized disease that may not require treatment other than excision. Large B-cell lymphoma with IRF4 rearrangement also typically occurs in children and young adults, involving Waldeyer ring or cervical lymph nodes, with a follicular or diffuse pattern of intermediate-to-large follicle-center B cells that aberrantly coexpress the post–germinal-center protein IRF4/MUM1. In contrast to pediatric-type follicular lymphoma, patients with large B-cell lymphoma with *IRF4* rearrangement typically require combination immunochemotherapy with or without local radiation.

Management of localized follicular lymphoma

Limited-stage (Ann Arbor I or II) FL is relatively uncommon and, as a result, there are no randomized studies indicating the optimal management strategy. Rather, most of the data are observational. Older studies suggested a proportion of patients might be cured with external beam radiation. MacManus and Hoppe (1996) found that ~40% of limited-stage patients with FL remained disease-free at 10 years after radiation treatment; late relapses beyond 10 years were unusual. Other studies also reported over 90% of patients achievement of a complete response and a 10-year disease-free survival (DFS) rate of ~40% to 50%, suggesting that cure is possible with this approach in a proportion of patients. Given the excellent long-term outcomes for patients with localized FL, there is concern for late-onset radiation-induced complications, including second primary cancers. Recent data indicate that radiation fields can be reduced without adversely impacting disease control. As a result, contemporary strategies tend to utilize an involved-site approach. Studies evaluating chemotherapy plus radiation (combined modality therapy [CMT]) have demonstrated improved PFS without an obvious effect on OS. Therefore, the CMT approach is likely best reserved for the rare patient who presents with bulky (node >7 cm) limited-stage FL. An Australian randomized trial (TROG 99.03) of systemic therapy after involved-field radiotherapy (IFRT) in early-stage FL revealed R-CVP (rituximab, cyclophosphamide, vincristine, prednisone) after IFRT reduced relapse outside radiation fields and significantly improved PFS. Finally, an alternative management strategy for this patient population is surveillance alone. A Stanford report of stage I and II patients, who received no initial therapy, showed that more than half of the 43 patients did not require therapy at a median of 6 years and that 85% of patients were alive at 10 years. However, a SEER analysis of 6568 patients with localized grade 1-2 FL found that upfront radiotherapy was associated with improved disease-specific survival (DSS) and OS compared to patients who did not receive RT (10 y and 20 y DSS 79% and 63% for RT versus 66% and 51% for no RT). A report from a large observational database found that the following treatment approaches were utilized for 471 stage I FL patients: rituximab combined with chemotherapy 28%, RT 27%, observation 17%, CMT 13%, rituximab 12%, and other 3%. Approaches utilizing systemic therapy produced better PFS outcomes than RT alone, but there were no OS differences between any of the approaches; therefore optimal management should be personalized for the patient.

Approach to patients with advanced-stage follicular lymphoma

Patients with advanced-stage FL are considered incurable with standard chemotherapy. The disease generally is responsive to treatment, however, and there are numerous effective treatment options. As a result, the prognosis is excellent relative to other cancers. A typical patient undergoes a number of different treatments, often separated by several years, and the goal of management is to achieve a normal life expectancy. Advanced-stage FL can be thought of as a chronic disease that requires long-term management, and the management is largely a matter of determining how to sequence the different therapies.

The approach to a newly diagnosed patient needs to be individualized, factoring in the presence or absence of symptoms, tumor burden, patient age and comorbidities, and goals of therapy. A 2 × 2 table can be constructed to help with the initial approach of separating patients by symptoms and tumor burden (Table 22-9). Using this approach, 4 patient categories are generated: (1) asymptomatic, low tumor burden; (2) asymptomatic,

Table 22-9 Algorithm for the approach to the newly diagnosed FL patient

	Low tumor burden	High tumor burden
Symptoms absent	Surveillance	R-chemotherapy +/− MR or O-chemotherapy +/− MR or rituximab monotherapy or surveillance in older/less fit patients
Symptoms present	Single-agent rituximab, low-dose radiation to single symptomatic site of disease, or R-chemotherapy	

O, obinutuzumab; R, rituximab.

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high tumor burden; (3) symptomatic, low tumor burden; and (4) symptomatic, high tumor burden. Patients with asymptomatic, low tumor burden should be followed with surveillance alone. Patients with asymptomatic, high-tumor-burden FL should generally start therapy soon after diagnosis, although selected patients may be observed initially, such as the very elderly or those who just meet the high-tumor-burden criteria (eg, 3 nodes in the 3- to 4-cm range). Patients with symptomatic, low-tumor-burden disease do benefit from therapy, often with mild treatment approaches including rituximab alone or low-dose radiation. From a decision-making standpoint, patients with symptomatic, high-tumor-burden FL are the most straightforward as they require treatment, while some also consider macroscopic involvement of cortical bone, kidneys and liver, and rapid progression over the preceding 3 months to be indicators of more aggressive disease, justifying the initiation of therapy. Treatment typically consists of chemoimmunotherapy, although there is little consensus on which specific chemoimmunotherapy regimen is best.

Management of asymptomatic, low-tumor-burden follicular lymphoma

Asymptomatic patients may be candidates for a strategy of surveillance alone. To determine whether observation is an option, one should assess the tumor burden. The GELF criteria (Table 22-10) are the most commonly used criteria to assess tumor burden and to assess eligibility for clinical trials. The surveillance strategy was first advocated at Stanford University when 2 retrospective studies suggested no detriment in patient outcome. Three randomized clinical trials in the prerituximab era later confirmed that low-tumor-burden FL patients assigned to surveillance alone experienced the same OS compared with patients assigned immediately to treatment. The median time to first chemotherapy in all studies was 2.3-3 years. More recently, a randomized trial compared surveillance alone with single-agent rituximab in patients with previously untreated, asymptomatic, low-tumor-burden FL. Patients were assigned to surveillance (arm A), rituximab at 4 weekly doses (arm B), or rituximab at 4 weekly doses plus a single dose every 2 months for 2 years (arm C). A significant prolongation in PFS and prolongation in the time to first chemotherapy was observed for the patients randomized to rituximab; however, there was no difference in OS at 3 years (95% in all arms), consistent with randomized trials in the prerituximab era. The study also evaluated quality of life (QOL). Given that these patients are symptom free, the main QOL issues tend to be anxiety, depression, and adjustment to illness. The study found that anxiety and depression were more common in patients with low-tumor-burden FL than in the general population but were still relatively infrequent at 13% and 3%, respectively. Patients in all treatment arms adapted to their illness over time. The patients identified as "anxious" adapted more readily when assigned to rituximab treatments. It is reasonable to conclude that, given no OS difference observed to date, surveillance remains the appropriate standard for the asymptomatic, low-tumor-burden FL population, though rituximab monotherapy can be considered in selected patients.

If administering single-agent rituximab to a patient with low-tumor-burden FL, should one utilize a maintenance strategy or simply retreat at progression? This dosing question was addressed in the RESORT study. After induction therapy with single-agent rituximab, patients with low-tumor-burden indolent B-cell NHL were randomized to receive maintenance rituximab (MR) once every 3 months until treatment failure or to be periodically retreated with rituximab (retreated with 4 weekly doses at each progression) until treatment failure. The trial revealed no difference in the time-to-treatment failure between the 2 dosing strategies. Patients on the maintenance arm, however, utilized 4 times as much rituximab. There was no difference in quality of life, depression, or anxiety between the 2 strategies. Based on these results, a retreatment strategy is preferred if opting for single-agent rituximab in this patient population.

Table 22-10 GELF criteria for high tumor burden

Any nodal or extranodal mass >7 cm
Three or more nodal sites with diameter of >3 cm
Elevated LDH
Hb <10 g/dL, ANC $<1.5 \times 10^9$/L, Plts $<100 \times 10^9$
Spleen >16 cm by CT scan
Risk or organ compression or compromise
Significant serous effusions

Meeting any 1 criterion qualifies as high tumor burden. All must be absent to qualify as low tumor burden.

ANC, absolute neutrophil count; Hb, hemoglobin; Plts, platelets.

Therapy for symptomatic and/or high-tumor-burden follicular lymphoma

Treatment is indicated for FL when patients develop adverse symptoms related to their disease, or develop bulky disease which is at high risk for causing symptoms or obstruction in the near future. The addition of rituximab to conventional chemotherapy, has improved outcomes in FL, including response rates, PFS, event-free survival (EFS), and OS. Table 22-11 summarizes major studies combining rituximab with chemotherapy.

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Table 22-11 Randomized trials of chemotherapy versus R-chemotherapy in high-tumor-burden, advanced-stage follicular lymphoma

Study	Treatment	*N*	Median follow-up	ORR	Time to event	OS
Hiddemann et al, *Blood*. 2005	R-CHOP vs CHOP	223 vs 205	1.5 years	96% vs 90%	88% vs 70% (2-year DOR)	95% vs 90% (2-year OS)
Marcus et al, *J Clin Oncol*. 2008	R-CVP vs CVP	162 vs 159	4.5 years	81% vs 57%	38 months vs 14 months (median DOR)	83% vs 77% (4-year OS)

Clearly, rituximab added to chemotherapy is a therapeutic advance in FL, though the optimal chemotherapy backbone remains unsettled. Data generated prior to the introduction of bendamustine in the United States indicated the most commonly used regimens in the United States were R-CHOP (60%), R-CVP (27%), and R- fludarabine-based (13%). A randomized comparison (FOLL5) of these regimens indicated R-CHOP had the best risk-benefit profile because it was more active than R-CVP and less toxic than R-FM. Subsequently, however, bendamustine, an alkylating agent with nucleoside analog properties, gained widespread adoption as the chemotherapy platform of choice in FL. A phase 3 trial comparing bendamustine plus rituximab (BR) to R-CHOP demonstrated better efficacy and reduced toxicity with BR. In this multicenter phase 3 study, 549 patients with high-tumor-burden indolent NHL and MCL (median age 64 years) were randomized to receive bendamustine 90 mg/m^2 on days 1 and 2, with rituximab 375 mg/m^2 on day 1, every 28 days (the BR group) or to receive standard R-CHOP chemotherapy every 21 days (the R-CHOP group). The overall response rates (ORRs) were similar in the BR and R-CHOP groups (92.7% versus 91.3%, respectively), but the CR rate was significantly higher in the BR group (39.8%) compared with the R-CHOP group (30.0%) (P = 0.03). When evaluating just the FL patients, with a median follow-up of 45 months, the median PFS was significantly longer in the BR group compared with R-CHOP group (median PFS, not reached versus 40.9 months, P = 0.007). OS did not differ between both groups. There was less hematologic toxicity, alopecia, infections, peripheral neuropathy, and stomatitis with BR. Drug-associated erythematous skin reactions were seen more frequently in the BR group. These data suggest that BR is a better option for untreated high-tumor-burden FL.

A confirmatory randomized phase 3 trial (BRIGHT study) was conducted in North America. Previously untreated indolent NHL patients with high tumor burden were randomized to BR or R-CHOP/R-CVP. Control arm patients were identified as R-CHOP or R-CVP candidates prior to randomization. The primary endpoint was to show noninferiority of BR in the CR rate. Seventy percent of the 447 enrolled patients had FL, and, in these patients, BR therapy was found to be noninferior to the R-CHOP/R-CVP control arm for CR rate (30% versus 25%) and overall response rate (99% versus 94%). Time-to-event data were not reported. Side-effect profiles were distinct, with more gastrointestinal toxicity and rash with BR and more neuropathy and alopecia with R-CHOP/R-CVP. Although, the BRIGHT data do not exactly replicate the StIL data for BR, they do suggest that BR remains a very reasonable alternative to R-CHOP or R-CVP in FL.

The question of whether to administer maintenance rituximab after frontline R-chemotherapy was addressed in the phase 3 PRIMA trial. The study evaluated the efficacy and safety profile of maintenance rituximab in newly diagnosed FL patients who responded to initial treatment with rituximab plus chemotherapy. Chemotherapy backbone was selected by treating center: R-CHOP (75%), R-CVP (22%), or R-FCM (3%). Patients were randomized to observation or to a single dose of rituximab every 2 months for 2 years. At a median follow-up of 36 months from randomization, the 2-year PFS in the maintenance rituximab arm was 75% versus 58% in the observation arm (P < 0.0001). The beneficial effect of maintenance rituximab was seen irrespective of the induction chemotherapy backbone and in both CR and partial remission (PR) patients. Grade 3-4 adverse events were slightly higher in the maintenance rituximab arm (24% versus 17%). No difference in OS was observed. Given the lack of OS benefit, the decision regarding the use of maintenance rituximab can be individualized. Rituximab administration does carry a low risk for neutropenia and low-grade infections, rarely, more serious toxicities, such as progressive multifocal leukoencephalopathy. As maintenance, rituximab generally is well tolerated and it has become a commonly utilized strategy in the United States.

The next-generation anti-CD20 monoclonal antibody obinutuzumab was compared with rituximab when combined with initial chemotherapy followed by maintenance in high-tumor-burden patients with follicular lymphoma in the GALLIUM study. A total of 1202 patients were randomized to obinutuzumab-chemo followed by obinutuzumab maintenance, versus rituximab-chemo followed by rituximab maintenance. Choice of chemotherapy backbone was at the discretion of participating centers and included bendamustine (57%), CHOP (32%), and CVP (10%). Dosing was different for the 2 antibodies, with

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obinutuzumab patients receiving more monoclonal antibody. Rituximab was administered at the standard dose of 375 mg/m^2 on day 1 of each chemoimmunotherapy cycle, while obinutuzumab was dosed at 1000 mg on days 1, 8, and 15 during cycle 1, and then on day 1 of subsequent chemoimmunotherapy cycles. Maintenance was administered at the same dose of the respective antibodies every 2 months for up to 2 years. The study showed no difference in overall or complete response rate between the 2 antibody strategies at the end of induction. During the maintenance period, however, a PFS benefit emerged in favor of obinutuzumab therapy with 3-year PFS of 80.0% versus 73.3%, and a hazard ratio of 0.66 (95% confidence interval, 0.51-0.85, $P = 0.0001$), though this advantage was driven by the infection related toxicity associated with the bendamustine subgroup and by patients younger than age 60. There was no difference in OS, and toxicity was increased in the obinutuzumab arm with higher rates of neutropenia and infusion-related reactions. Based on these data, obinutuzumab-based chemoimmunotherapy plus maintenance is now a United States Food and Drug Administration (FDA)-approved initial treatment option for high-tumor-burden FL patients, but, in the absence of an OS benefit and with increased toxicity, rituximab-based therapy also continues to be an acceptable alternative. Chemotherapy-free treatment has been tested in lieu of chemotherapy as initial therapy for FL. The RELEVANCE trial compared R-lenalidomide (R2) to R-chemotherapy (72% R-CHOP) in 1030 patients with FL (50% high-risk FLIPI; 13% grade 3A; 40% bulky >7 cm disease). It demonstrated similar response rates and PFS between R2 and chemoimmunotherapy (R2: ORR 86%, CR 48%, 3-year PFS of 77%; R-chemo: ORR 92%, CR 53%, 3-year PFS 78%). This randomized trial confirmed similar efficacy of R2 to chemoimmunotherapy and has been added to NCCN guidelines for first-line therapy although not FDA approved for frontline treatment of FL.

Therapy for relapsed and refractory follicular lymphoma

Multiple options exist for the treatment of patients who have progressed after first-line therapy, and the decision of which therapy to use depends on a number of factors, including the prior treatment utilized, duration of prior response, patient age, comorbid illnesses, and goals of therapy. Options range from low-risk strategies, such as single-agent rituximab, to higher intensity strategies, such as autologous or allogeneic stem cell transplantation, with many options in between.

The RESORT study specifically addressed rituximab retreatment in low-tumor-burden FL wherein previously untreated low–tumor burden FL received 4 doses of rituximab, and responding patients were randomly assigned to either retreatment with rituximab (RR) or maintenance rituximab. Patients receiving RR were eligible for retreatment at each disease progression while those assigned to MR received rituximab every 3 months until treatment failure. This study demonstrated no significant difference in median time-to-treatment failure between these strategies but moreover, of the patients who received RR at first progression, 61% responded with a median response duration of 18.5 months.

A report from the National LymphoCare Study shows that patients who relapse within 2 years of initial chemoimmunotherapy have a significantly inferior overall survival compared to patients with longer initial remissions. Population-based data from the United States and validated in France establish that 80% of patients who achieve an initial remission longer than 2 years have a predicted life expectancy comparable to age-matched controls without lymphoma.

These high-risk patients with early progression of disease constitute an unmet medical need within relapsed FL and warrant evaluation in clinical trials of novel treatment approaches.

Bendamustine is approved in the United States for use in patients with rituximab-refractory indolent B-cell lymphoma. A pivotal trial in 100 patients reported an objective response rate of 75% with a median PFS of 9.3 months. A subsequent randomized trial (GADOLIN) compared bendamustine alone to bendamustine combined with obinutuzumab, followed by obinutuzumab maintenance, in rituximab-refractory FL. Patients treated with obinutuzumab-bendamustine demonstrated an improved PFS and OS compared to bendamustine alone, making this a preferred option in rituximab-refractory patients. An important caveat is that patients in this trial were bendamustine naïve, so this strategy has not proven beneficial in patients already treated with bendamustine therapy in the frontline setting.

Novel targeted therapies are playing an increasing role in the management of relapsed and refractory follicular lymphoma. The oral immunomodulating agent lenalidomide was evaluated as monotherapy or in combination with rituximab in CALGB 50401, a randomized trial for rituximab-sensitive FL, with lenalidomide -rituximab demonstrating an ORR and complete response rate of 76% and 39%, respectively, and a median time to progression of 2 years. The phase 3 randomized AUGMENT trial for patients with relapsed/refractory FL revealed a significantly improved PFS, 39.4 months versus 14.1 months, for lenalidomide plus rituximab versus placebo plus rituximab, respectively. Lenalidomide can now be considered an effective therapy for relapsed FL and is currently under evaluation as frontline therapy. Four targeted inhibitors of PI3K delta were available for patients with FL who relapsed after

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at least 2-3 prior lines of therapy, however all except copanlisib have been withdrawn from the market. We will detail the data for the approval of these agents however as of May of 2022 they are not available for patients with a diagnosis of FL. Idelalisib, a PI3 kinase delta isoform inhibitor, was the first of these kinase inhibitors to be studied with ORR of 57%, and median duration of response was 12.5months. Another PI3 kinase inhibitor, copanlisib, has similar response rates to idelalisib in relapsed FL. This intravenously delivered agent targets the PI3 kinase alpha and delta isoforms. A third PI3 kinase inhibitor, duvelisib, which targets the gamma and delta isoforms is also an active oral agent in patients with relapsed FL, with similar activity to idelalisib and copanlisib. Umbralisib is an oral inhibitor of multiple kinases, including PI3K delta and casein kinase. It is approved for relapsed FL after 3 lines of therapy on the basis of a multicenter phase 2 trial with an ORR of 45% and a median duration of response of 11 months. To date there is no compelling data showing superiority of one over another. All 4 PI3K inhibitors represent effective treatment options in multiply relapsed/refractory disease, but their use in therapy requires counseling and monitoring for their unique toxicity profiles. Common toxicities include infection, myelosuppression, and inflammatory toxicities such as pneumonitis and colitis. Prophylaxis against opportunistic infections is encouraged and cytomegalovirus reactivation can occur. Table 22-12 details the trials, outcomes, and common adverse events.

Tazemetostat is an oral inhibitor of EZH2 that has shown activity in a small nonrandomized phase 1/2 trial that included patients with multiply relapsed FL. Responses are seen in most patients with EZH2 mutations, found in approximately 20 percent of patients with FL, and to a smaller extent in patients with EZH2 wild-type FL. It is approved for relapsed or refractory EZH2 mutation positive FL who have received at least 2 prior systemic therapies or FL for which there are no satisfactory alternative options. Data from open-label single-arm phase 1/2 trial reveal an ORR of 69% in EZH2 mutated FL with a median duration of response (DOR) of 11 months and median PFS of 14 months, while in EZH2 wild-type FL the ORR was 35% with a median DOR of 13 months and median PFS of 11 months. Common toxicities include fatigue, upper respiratory tract infection, musculoskeletal pain, nausea, and abdominal pain and there is an increased risk of secondary hematolgic malignancies with tazemetostat.

Radioimmunotherapy is also an option for patients with indolent B-cell NHL if the bone marrow is minimally involved and the disease is not bulky. With Y^{90} ibritumomab tiuxetan, response rates are ~70% and response duration is, on average, 11-15 months. Single-agent rituximab can be used in relapsed lymphoma, although now that most patients have received it with their primary therapy, and often as maintenance therapy, more and more patients are becoming rituximab-refractory. For patients who are still rituximab-sensitive, single-agent rituximab is an attractive option for elderly or unfit patients.

Chimeric antigen receptor T (CART) cell therapy and stem cell transplantation is a treatment option for patients with multiply relapsed FL and is discussed in Chapter 24.

Marginal zone lymphomas

The WHO classification separates the marginal zone B-cell lymphomas (MZLs) into extranodal MZL of MALT type, nodal MZL, and splenic MZL (SMZL). The morphology of these disorders is characterized by an infiltrate of centrocyte-like small cleaved cells, monocytoid B cells, or small lymphocytes; these disorders may exhibit an expanded marginal zone surrounding lymphoid follicles. The immunophenotype is characterized by expression of CD20 but lack of CD5 or CD10 expression (Table 22-2); this marker profile is useful in distinguishing MZL from SLL, MCL, and FL. A feature common to many cases of MZL is association with chronic antigenic stimulation by microbial pathogens or autoantigens as described previously. Examples include gastric MALT (*H pylori*), cutaneous MALT (*B burgdorferi* or *afzelii*), ocular adnexal MALT (*C psittaci*), nodal MZL (hepatitis C), SMZL (hepatitis C), pulmonary or parotid MALT (Sjögren syndrome), and thyroid MALT (Hashimoto thyroiditis). There is significant geographic variation associated with certain microbial pathogens. For example, the prevalence of *C psittaci* in patients with ocular adnexal MALT appears to be 50% to 80% in Italy, Austria, Germany, and Korea, whereas this organism is observed infrequently in Japan, China, and the United States.

MALT lymphomas

Extranodal MZLs or MALT lymphomas constitute ~70% of all MZLs. They occur most commonly in mucosal sites, predominantly gastric or intestinal, as well as lung, salivary gland, ocular adnexa, skin, and thyroid, among others. These sites often are affected by chronic infection or inflammation in the setting of autoimmune disease, such as Sjögren syndrome or Hashimoto thyroiditis. The typical presentation of MALT lymphoma is an isolated mass in any of these extranodal sites or an ulcerative lesion in the stomach. Clinically, these lymphomas are typically indolent, with 10-year OS rates in excess of 90% in many series. MALT lymphomas can be characterized as gastric (30%-40%) or nongastric (60%-70%), and the approach to disease management is site-specific. Approximately 90% of gastric MALT lymphomas are associated with *H pylori* infection. Newly diagnosed patients typically report dyspepsia, pain, reflux symptoms, or weight loss. Upper endoscopy can reveal erythema, erosions, ulcers,

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Table 22-12 PI3K trials, outcomes, and common adverse events

	Umbralisib*	Idelalisib*	Copanlisib	Duvelisib*
Citatiton	2021 JCO Fowler	2014 NEJM Gopal	2019 AJH Dreyling	2019 JCO Flinn
Trial Description	UNITY-NHL – FL cohort N = 208 Total N = 117 FL	DELTA – FL cohort N = 125 Total N= 72 FL	CHRONOS-1 – FL Cohort N = 142 total N = 104 FL	DYNAMO – FL cohort N = 129 Total N = 83 FL
Median Follow-up	27.5 months	19.4 months	12.5-42.6 months (efficacy): safety:6.7 mo	32.1 months
Median Exposure	7.6 (1.0 -27)	6.5 (0.6 - 31.0)	Not reported	6.7 (0.4 - 45.5)
Discontinuation	77% 12% due to AEs	90.3% 20.8% due to AEs	92.3% 26.8% due to AEs	51.2%[1] 24% due to AEs
ORR	45.3%	55.6%	58.7%	42.2%
CR	5%	13.9%	20.2%	1.2%
PR	40%	41.7%	38.5%	41%
Median DOR	11.1 months (range 8.3-15.6)	10.8 months (range 0-26.9)	14.1 months (range 0.03-42.5)	10 months (range 6.5-10.5)
AEs of Interest				
ALT Increase (all-grades)	33%	73 (50%)	177 (40%)	32/141 (23%)[4]
ALT Increase (Gr ≥3)	8%	27 (18%)	34 (8%)	2/141 (1.4%)[4]
AST Increase (all-grades)	32%	60 (41%)	163 (37%)	39/141 (28%)[4]
AST Increase (GR ≥3)	7%	18 (12%)	24 (6%)	2/141 (1.4%)[4]
Colitis (all-grades)	2%			NR
Colitis (Gr ≥3)	NR			
Diarrhea (all -grades)	58%	68 (47%)[2]	222 (50%)[2]	60/168 (36%)
Diarrhea (Gr ≥3)	10%	20 (14%)[2]	101 (23%)[2]	8/168 (5%)
Pneumonia (all-grades)	6%	37 (25%)[3]	91 (21%)	35/168 (21%)[5]
Pneumonia (Gr ≥3)	NR	23 (16%)[3]	67 (15%)	23/168 (14%)[5]
Pneumonitis (all-grades)	<1%	NR[3]	NR	15/168 (9%)
Pneumonitis (Gr ≥3)	NR			NR
Rash (all-grades)	18%[6]	31 (21%)	136 (31%)	26/168 (15%)
Rash (Gr ≥3)	3%[6]	4 (3%)	41 (9%)	3/168 (1.7%)

* The FDA's Oncologic Drugs Advisory Committee (ODAC) met on April 21, 2022 and voted 16-0 with a single abstention to recommend that future approvals of PI3K inhibitors for patients with hematologic cancers be supported by randomized clinical data. The companies making Umbralisib, Idelalisib and Duvelisib voluntarily withdrew these drugs from the market for the treatment of FL.

1 = Discontinuation rate of all cohorts combined. MZL cohort specific data not reported
2 = Colitis and diarrhea events reported together
3 = includes pneumonia and pneumonitis events
NR = not reported as occurring in ≥10% of patients
4 = ALT/AST rates not reported in pooled analysis, rates reported are from a phase 2 clinical trial of 141 patients
5 = includes all lower respiratory tract infections
6 = Rash includes maculopapular rash, erythematous rash, pruritic rash, macular rash
AST – Aspartate aminotransferase
ALT – Alanine transaminase
Gr – grade

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or masses. A consistent observation has been that 70% to 80% of gastric MALT lymphomas durably regress following effective *H pylori* antibiotic therapy. The most widely used antibiotic regimen is a combination of amoxicillin, omeprazole, and clarithromycin. Metronidazole is an effective alternative antibiotic in patients with a penicillin allergy. Lymphoma responses can be slow, taking as long as 6 months to 1 year. Repeat assessment of *H pylori*, by histologic examination or a urea breath test, is necessary to ensure that the bacteria have been eradicated. The strongest predictor for lymphoma nonresponse to antibiotic therapy is the presence of the t(11;18) translocation, which is present in 20% to 30% of cases. In the series reported by Nakamura et al, only 3 of 30 patients with t(11:18) experienced lymphoma regression following *H pylori* eradication therapy. In patients who do not respond to antibiotics, or in *H pylori*–negative cases, IFRT has been highly effective with DFS or PFS rates of >90% at 10 years. The prognosis for early-stage gastric MALT is excellent, with most series reporting 10-year OS rates in excess of 90%. For patients with advanced-stage disease, regimens similar to those used in FL, including rituximab alone or in combination, can be used. Transformation to DLBCL is possible, but a remarkable observation has been the regression of early-stage *H pylori*–positive gastric-diffuse large B-cell lymphomas with *H pylori* eradication therapy. This observation was noted in DLBCL clearly arising from gastric MALT (transformation) and in de novo DLBCL (no apparent underlying MALT).

Nongastric MALT lymphomas also have an indolent course, including the one third of patients who present with stage 4 disease. OS at 10 years exceeds 90% in many series. The most common locations are the salivary glands (26%), ocular adnexa (17%), skin (12%), lung (8%), upper airways (7%), thyroid (6%), and intestinal tract (5%). Treatment approaches depend on both stage and site of primary involvement and may include surgery, radiation therapy, or chemotherapy. Radiation therapy produces excellent results in limited-stage disease. Many patients can be managed with surveillance alone if asymptomatic. Patients with advanced-stage disease typically can be managed using the same principles used for FL. Patients often have a low disease burden, and rituximab monotherapy may be highly effective. For high-tumor-burden patients or those progressing on rituximab alone, rituximab added to chlorambucil was shown to improve EFS in an randomized controlled trial compared to chlorambucil alone. Recurrences tend to occur in the same or other extranodal locations. For patients requiring chemoimmunotherapy, bendamustine has been employed with success, as with FL. Recently the Bruton's tyrosine kinase inhibitor ibrutinib was FDA-approved for relapsed/refractory marginal zone lymphoma based on a 63-patient phase 2 trial for relapsed/refractory marginal zone lymphoma of any subtype. The oral dose was 560 mg daily. Ibrutinib produced an ORR of 48% with a median PFS of 14.2 months, making this an appealing available option for patients with relapsed marginal zone lymphoma.

Nodal MZL

Nodal MZL also arises from marginal zone B cells but presents with nodal involvement akin to FL. Whenever nodal MZL is diagnosed, a careful history review and a physical examination should be conducted to determine if a coexisting extranodal MALT lymphoma component exists, as concurrent disease may be present in up to one third of cases. Nodal MZL more commonly presents at advanced-stage (Ann Arbor stage III-IV) than with MALT-type MZL. The t(11;18) karyotypic changes identified in MALT are absent in nodal MZL, and no specific or recurring karyotypic anomaly has been described. IgM monoclonal gammopathy can occur in ~10% of cases. Hepatitis C virus infection is reported in up to 25% of patients. Across reported series, the 5-year OS for nodal MZL is 60% to 70%; however, the EFS is only 30%, which likely reflects more commonly encountered advanced-stage disease. Management is similar to the approach recommended in FL, and ibrutinib is available as an option at relapse, as reviewed previously. Of note while the subanalysis from the AUGMENT trial in 63 relapsed/refractory MZL showed no advantage over rituximab monotherapy (though limited by sample size and imbalance in baseline prognostic factors), subsequent approval of R2 for MZL arose from the MAGNIFY trial where MZL patients achieved an ORR of 65%, CR of 38% and median PFS of 38.4 months. While the PI3K inhibitors umbralisib, idelalisib and copanlisib have all shown activity in MZL, only umbralisib is approved for treatment of relapsed MZL after 1 line of anti-CD20 monoclonal antibody containing regimen attributable to demonstration of a 49% ORR and median DOR not yet reached.

In the updated WHO classification, a new category, pediatric nodal MZL, which has distinctive clinical and morphologic characteristics, was introduced. There is a male predominance (20:1), and patients usually present with localized asymptomatic adenopathy in the head and neck region. Morphologically, the infiltrate is similar to that seen in adults, except that progressively transformed germinal centers often are seen.

Splenic MZL

Splenic MZL presents at a median age of 68 years and is more common in females. Patients usually present with

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symptomatic splenomegaly, and involvement of the peripheral blood and bone marrow are common. Generalized lymphadenopathy is rare, but patients may have splenic hilar nodal or hepatic involvement. Patients may have concomitant autoimmune cytopenias, which should be considered in patients with anemia or thrombocytopenia at diagnosis. Diagnosis usually is based on spleen histology following splenectomy or after bone-marrow examination. Clinically, SMZL can be confused with CLL, MCL, FL, HCL, or WM. Unlike CLL and MCL, SMZL is typically CD5-negative, and, unlike FL, it is CD10-negative. Unlike HCL, which is CD103-positive and replaces the splenic red pulp, SMZL is CD103-negative and replaces the splenic white pulp. *MYD88* mutation may be useful in distinguishing SMZL from WM, where the mutated gene is found in most cases of WM and only rare cases of SMZL. A prognostic model, using hemoglobin <12 g/dL, elevated LDH, and albumin <3.5 g/dL, has identified 3 distinctive risk groups (low, intermediate and high). OS at 5 years was 88%, 73%, and 50% for patients with 0, 1, and 2 or 3 risk factors, respectively, in the prerituximab era. All patients should be checked for underlying hepatitis C because antiviral therapy for hepatitis C often leads to regression of the SMZL and is the recommended initial treatment of choice in these patients. For non–hepatitis C patients, observation alone is the recommended initial approach for asymptomatic patients without bulky splenomegaly or significant cytopenias. For patients requiring therapy, splenectomy has long been considered the optimal first-line treatment. However, single-agent rituximab is also remarkably active, with an ORR approaching 100% in small series. In an observational retrospective study, rituximab produced more durable remissions than did splenectomy. For young patients, who are appropriate surgical candidates, splenectomy or rituximab monotherapy may be considered as initial therapy, whereas for elderly patients or patients otherwise unfit for surgery, rituximab monotherapy is preferred. Patients with subsequent relapses in need of therapy may be considered for splenectomy if not yet performed, retreatment with single-agent rituximab, or treatment with chemoimmunotherapy or ibrutinib.

Lymphoplasmacytic lymphoma and Waldenström macroglobulinemia

Lymphoplasmacytic lymphoma is defined in the WHO classification as an indolent neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells. The lymphoma cells may express B-cell markers CD19 and CD20 and are CD5- and CD10-negative, much like the MZLs (Table 22-3). LPL with production of an IgM paraprotein produces the syndrome known as Waldenström macroglobulinemia, which is described further in Chapter 25.

Hairy cell leukemia

HCL is an indolent B-cell lymphoproliferative disorder accounting for only 2% of all leukemias; it is characterized pathologically by neoplastic lymphocytes with cytoplasmic "hairy" projections on the cell surface, a positive tartrate-resistant acid phosphatase stain, and an immunophenotype positive for surface immunoglobulin, CD19, CD20, CD22, CD11c, CD25, and CD103 (Table 22-2). Marrow biopsy demonstrates a mononuclear cell infiltrate with a "fried egg" appearance of a halo around the nuclei and increased reticulin and collagen fibrosis. Nearly 100% of cases harbor the *BRAF* V600E mutation, abnormally activating the BRAF-MEK-ERK pathway.

HCL is 4 times more common in men than in women and presents at a median age in the 50s with pancytopenia and splenomegaly. Most patients have an absolute monocytopenia, which may be a clue to the diagnosis. The bone marrow aspirate is often a dry tap due to increased marrow reticulin. Making the proper diagnosis is crucial because of HCL's generally favorable prognosis, with a 10-year OS exceeding 90% and an excellent treatment response to nucleoside analogs. Most patients with HCL require therapy to correct cytopenias and associated complications, in addition to the presence of symptomatic splenomegaly. If a patient is asymptomatic and cytopenias are minimal, the patient may be observed initially. HCL is uniquely sensitive to purine analogs. The nucleoside analogs cladribine or pentostatin are the treatments of choice in HCL in view of the high response rates and durable remissions achieved. Cladribine is used more commonly because of the short duration of therapy required; cladribine also is available as a subcutaneous injection. In one large series of 233 patients with long-term follow-up, the ORR and CR rates with either of these agents were 97% and 80%, respectively. The median recurrence-free survival was 16 years, and many of the relapses were observed 5 to 15 years after initial treatment, highlighting the unique natural history of this disease. It currently is recommended that assessment of response should be determined 4 to 6 months after the end of treatment; a second course can be given only if a PR is attained. Rituximab given concurrently with cladribine potentially improves both CR rates and reduces detection of measurable residual disease (MRD). A recent study evaluating rituximab/cladribine versus cladribine monotherapy revealed CR rates were 100% versus 88%, MRD-free CR rates 97% versus 24% and blood MRD-free rates 100% versus 50% respectively. At 96 months median follow-up, 94% in the rituximab/cladribine versus

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12% in the cladribine alone arm remained MRD-free. A central question not yet answered is whether MRD affects long-term outcome in HCL like other hematologic malignancies. Patients who relapse after frontline nucleoside analog therapy are often retreated with a nucleoside analog with similarly high response rates. Rituximab may also be administered for relapsed disease. For multiply relapsed patients, the anti-CD22 antibody drug conjugate moxetumomab pseudotox-tdfk is FDA approved for HCL relapsed after at least 2 prior therapies including a purine analog. Among 80 patients treated, the ORR was 75%, and the rate of durable CR (at least 180 days) was 30%, For the uncommon patients with relapsed HCL, who are refractory to both nucleoside analogs and rituximab, *BRAF* inhibitors have also demonstrated high response rates as single agents and should be considered in these selected cases. The role of the BRAF-inhibitor vemurafenib is being explored in the upfront setting for HCL and has shown promising response rates.

HCL-variant is a distinct disease categorized separately in the WHO classification, and, despite its name, it is considered to be unrelated to HCL. HCL-variant does not harbor the *BRAF*-V600E mutation. It differs from HCL in the lack of monocytopenia and by the presence of an elevated white blood cell count. The bone marrow is easier to aspirate because the reticulin fiber content is low. The immunophenotype of HCL-variant also differs in that the cells are CD25-negative. CD103 is expressed infrequently and CD11c is usually positive. Unlike HCL, HCL-variant responds poorly to purine analogs. Splenectomy can result in partial remissions, and some patients can respond well to rituximab.

Transformation to aggressive lymphoma in indolent lymphomas

Histologic transformation (HT) is the development of aggressive NHL in patients with an underlying indolent lymphoma and approximately 15 percent of patients with FL undergo HT during their disease course at an estimated annual rate of 1% to 2%. It most commonly occurs in FL but can occur in any of the indolent lymphomas. The British Columbia Cancer Agency reported on 600 patients with FL who subsequently developed HT and in their series, the annual risk of transformation was 3% per year, with 10- and 15-year risks of 30% and 45%, respectively. Risk factors for subsequent HT at the time of initial presentation of FL were evaluated among over 2600 patients prospectively enrolled in the National LymphoCare Study where median follow-up was 6.8 years and HT was identified clinically or pathologically in 14%. The following factors were associated with an increased risk of confirmed or suspected HT:

- >1 extranodal site – hazard ratio (HR) 1.39
- ECOG performance status >1 – HR 2.12
- Increased serum level of LDH – HR 1.57
- Systemic "B" symptoms (fevers, night sweats, weight loss) – HR 1.35.

Other studies have reported on risk factors which include advanced-stage, increased LDH, grade III histology, high FLIPI or IPI score, lack of CR following initial treatment, and early treatment failure (progression within 24 months of chemoimmunotherapy). FDG-PET imaging can be helpful in selecting a biopsy site when establishing HT, but bright FDG avidity alone does not establish a diagnosis of HT, nor does increased uptake on pretreatment PET imaging predict future HT. Histologically, DLBCL is the most frequently observed subtype. One should assay for MYC and BCL-2 by FISH and by immunohistochemistry. The treatment is directed at the aggressive lymphoma and depends on a variety of factors, including age, comorbidities, and extent of prior treatment for FL. Patients with HT, who have never received R-CHOP, have a cure rate similar to de novo DLBCL, making R-CHOP the treatment of choice in most patients. Consideration for stem cell transplantation consolidation is warranted in selected patients.

KEY POINTS

- Follicular NHL is the most common indolent NHL.
- Patients with asymptomatic, advanced-stage indolent NHL may be followed without specific therapy to assess the pace of disease, or single-agent rituximab may be used to delay the use of systemic chemotherapy.
- Anti-CD20 antibody therapy plus chemotherapy is recommended in patients with symptomatic or high-tumor-burden disease by the GELF criteria.
- Maintenance anti-CD20 antibody therapy improves PFS with no impact on OS.
- There are a multitude of therapeutic options for relapsed indolent lymphoma, including novel targeted agents and stem cell transplantation.

Indolent peripheral T-cell lymphomas

Peripheral T-cell lymphomas (PTCLs) represent 10% to 15% of all NHLs in Western populations and are a heterogenous group of mature T-cell neoplasms arising from postthymic T

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cells at various stages of differentiation. NK-cell lymphomas are included in this group because of the close relationship between these 2 cell types. The importance of the T-cell phenotype and the impact on prognosis are now well established but are relatively recent advances. A large retrospective study, the International T-Cell Lymphoma Project (ITLP), collected 1153 cases of PTCLs from 22 centers from around the world and highlighted the geographic, clinicopathologic, and prognostic differences of this diverse group of diseases. There is a range of diseases among T- and NK-cell neoplasms, with most diseases behaving aggressively; however, a minority have a favorable prognosis or an indolent course (Table 22-3).

Indolent PTCLs

Mycosis fungoides and Sézary syndrome

In contrast to nodal NHLs, which are mostly B-cell derived, ~75% of primary cutaneous lymphomas have a T-cell phenotype and two thirds are mycosis fungoides or Sézary syndrome (SS). MF is an epidermotropic, primary cutaneous T-cell lymphoma and represents the most common of all primary cutaneous lymphomas (50%). MF usually has an indolent course, but, like indolent B-cell lymphomas, it is considered incurable using conventional therapies. MF is limited to the skin in its early phases and appears as plaques or patches; but, with time, it evolves to diffuse erythroderma or cutaneous nodules or tumors, usually with associated adenopathy. The early-stage lesions appear characteristically in a bathing suit distribution and are often pruritic in nature. Extracutaneous disease can occur in advanced stages and may indicate histologic transformation. The histology varies with stage of the disease, but epidermotropism is seen with typical plaques and intraepidermal collections of so-called Pautrier microabscesses. The T cells are $CD4^+/CD8^-$, often with aberrant loss of 1 or more of the T-cell antigens CD2, CD3, CD5, and CD7. Progression to nodal disease, organ infiltration, and circulating clonal T cells (SS) represents the advanced stage of the disease. A unique clinical staging system has been proposed by the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) for MF and SS. The extent of cutaneous and extracutaneous disease is the most important prognostic factor in MF, with a 10-year disease-specific survival ranging from 97% to 98% for patients with limited patch/plaque disease (<10% of skin surface; stage I) to 20% for patients with lymph-node involvement.

SS is a distinct disorder characterized by erythroderma, generalized lymphadenopathy, and the presence of Sézary cells in the skin, lymph nodes, and peripheral blood. It is associated with an aggressive course with a 5-year OS rate of 20% to 30% with lower rates seen with high Sézary cell counts.

Because MF is incurable and the use of early therapy does not affect survival, a nonaggressive approach is recommended. Patients with stage IA disease may be managed expectantly with careful surveillance. If treatment is needed, topical steroids or topical nitrogen mustard, electron-beam radiotherapy, or cutaneous photochemotherapy with oral psoralen plus ultraviolet A typically are employed. Phototherapy with psoralen plus ultraviolet A or B is recommended for more widespread disease. Low-dose radiotherapy can be helpful to improve symptoms and cosmesis. Patients with progressive disease and those with systemic dissemination may be appropriately treated with methotrexate or corticosteroids, although responses are usually brief.

Combination chemotherapy regimens are not particularly effective and provide only transient responses. Single-agent treatments are preferred, particularly with slowly progressive disease, because of a high risk of myelosuppression and infection and only modest response durations seen with combination chemotherapy. Gemcitabine (ORR 48%-75%), pentostatin (ORR 28%-71%), and liposomal doxorubicin (ORR 56%-88%) have single-agent activity. Alternatively, IFNa, bexarotene, vorinostat, romidepsin, and brentuximab vedotin all have efficacy in advanced-stage MF and SS. Brentuximab vedotin is preferred in CD30-positive cases based on the international phase 3 ALCANZA trial where 131 patients with CD30-positive relapsed/refractory MF or cutaneous T-cell lymphoma (CTCL) were randomized between the anti-CD30 antibody drug conjugate brentuximab vedotin, or the investigator's choice of oral methotrexate or oral bexarotene. Patients treated with brentuximab vedotin had significant improvement in the primary endpoint of objective response lasting at least 4 months (56.3% versus 12.5%), resulting in FDA-approval for brentuximab vedotin in this indication.

Bexarotene is an oral retinoid and is FDA-approved for cutaneous T-cell lymphoma. In a multicenter trial of 94 patients with advanced-stage MF/SS, the ORR was 45% but with only 2% CRs. The common toxicities are hypertriglyceridemia (82%) and central hypothyroidism (29%). The histone deacetylase inhibitors, vorinostat and romidepsin, are both approved for the treatment of CTCLs. Vorinostat is available orally and has an ORR of ~30% and a median duration of response of ~6 months. A phase 2 trial with romidepsin demonstrated an ORR of 35% (CR 6%) with a median DOR of 15 months in one study and 11 months in another. Side effects that are common

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with histone deacetylase inhibitors are fatigue, nausea, vomiting, neutropenia, and thrombocytopenia. Prolonged QT syndrome also can occur, and thus electrolytes should be monitored closely, and an electrocardiogram should be performed in high-risk patients during therapy. Alemtuzumab, the humanized monoclonal antibody targeting CD52, also has been used in MF and SS with some success; however, patients are at high risk of opportunistic infections. Studies evaluating low-dose alemtuzumab (10 mg thrice weekly) have been similarly effective with reduced toxicity, and should be preferred. Small studies also report single-agent activity for lenalidomide (ORR 28%) and low-dose pralatrexate given at 15 mg/m^2 for 3 of every 4 weeks (ORR 45%). Mogamulizumab (moga) is a defucosylated humanized antibody directed against the chemokine receptor CCR4, which is overexpressed on malignant T cells. Compared to vorinostat in the phase 3 MAVORIC trial, moga achieved superior PFS, response rate, and quality of life with acceptable levels of toxicity. For patients with MF, moga achieved superior PFS (hazard ratio 0.72; 95% CI: 0.51 to 1.01), but the advantage was even greater for patients with Sézary syndrome. It should be noted that the study excluded patients with transformed disease. Moga is approved by the FDA for treatment of adult patients with relapsed or refractory MF or SS after at least 1 prior systemic therapy. There is some data that suggests that after moga exposure, the risk of acute graft versus host disease in patients who undergo allogeneic hematopoietic stem cell transplant (HCT) within 6 months is increased, but this remains to be confirmed.

Allogeneic transplantation has been explored in selected cases of MF and SS. The European Group for Blood and Marrow Transplantation recently reported a multi-institutional retrospective study evaluating allo HCT (myeloablative and reduced intensity conditioning (RIC)) in 60 patients with MF (n = 36) or SS (n = 24). Almost half had refractory disease at the time of allo HCT; the median number of prior regimens was 4. With a median follow-up of 3 years, the 3-year PFS and OS were 34% and 53%, respectively, with higher survival rates observed in the RIC group (3-year PFS 52% versus 29%, P = 0.006).

Large-cell transformation in MF is defined as large cells in >25% of the infiltrate or as cells forming microscopic nodules. The incidence ranges from 8% to 39% and typically is associated with a poor prognosis, but there have been some long-term survivors. One study evaluated 100 cases of transformed MF; the median survival was 2 years with a 5-year OS and a disease-specific survival of 33% and 38%, respectively, compared to MF patients without transformation. The factors associated with a poor DSS were CD30-negative status, folliculotropic MF, generalized skin lesions, and extracutaneous transformation. Those cases with zero factors had a 2-year DSS of 83% compared with 14% to 33% in patients with 3 or 4 factors. The optimal management is unclear, but for young patients, systemic chemotherapy should be used and autologous or allogeneic transplantation should be considered particularly with high-risk disease. Consolidative radiation may be an option in local transformations.

Primary cutaneous ALCL

Primary cutaneous ALCL (C-ALCL) is part of a spectrum of diseases belonging to the category of primary cutaneous CD30$^+$ T-cell lymphoproliferative disorders that also includes lymphomatoid papulosis and "borderline" cases that have overlapping features of both disorders. C-ALCL is the second most common type of CTCL. Patients are typically older males (median age 60 years), presenting with a solitary nodule with multifocal disease occurring in only 20% of patients. Partial or complete spontaneous regression occurs in ~25% of cases. C-ALCL must be distinguished from systemic ALCL with secondary cutaneous involvement through staging procedures.

The outcome is very favorable with a 10-year DSS of 95%. It is notable that patients with localized C-ALCL with 1 draining lymph node involved have a similarly good prognosis. For localized C-ALCL, radiation is the preferred therapy. Progression to systemic involvement can occur in a minority of cases. For more advanced-stage cases, the best management is unclear. An argument can be made to treat minimally symptomatic patients conservatively with palliative dose radiotherapy just to the few most prominent lesions, but for patients where systemic therapy is required, brentuximab vedotin is preferred based on the aforementioned data for this agent in CD30$^+$ CTCL.

Breast implant–associated ALCL

ALCL associated with implants typically presents as an unexplained seroma or capsule thickening. The lymphoma typically involves the capsule only, without invasion of the breast tissue or formation of discrete mass lesions. Almost all cases are localized. The tumor cells are CD30$^+$ and ALK negative. The neoplastic cells float in the effusion fluid or the cells become embedded tissue; importantly, however, breast parenchyma usually is not involved, and the ALCL cells infiltrate the cavity containing the implant rather than the breast tissue directly. Breast implant–associated ALCL has been associated with both silicone and saline implants, but importantly, it occurs almost exclusively in implants with a textured, as opposed to a smooth, surface. A total

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capsulectomy should be performed, and, because bilateral cases have been reported, removal of the uninvolved breast implant is generally considered. The growing body of literature supports that ALK-negative ALCL in this setting appears to have an indolent clinical course with a favorable prognosis, and most patients can be observed following removal of the implant and capsule and will not require adjuvant therapy. Patients with disease limited to the effusion or confined to the capsule have a good/excellent prognosis with up to 93% reported to achieve complete remission at a median follow-up of 2 years. Presentation with a tumor mass that extends beyond the capsule, with lymph node or more distant involvement reflects aggressive disease and is associated with lower disease-free and overall survival. Mass-forming disease, lymph node involvement or distant disease may require systemic treatment, and this is advocated for stage 2-4 disease and can be treated similar to typical systemic ALK-negative ALCL.

T-cell large granular lymphocytic leukemia and chronic lymphoproliferative disorder of NK cells

T-cell large granular lymphocytic leukemia (T-LGL) is defined by a persistent (>6 months) increase in the number of peripheral-blood large granular lymphocyte cells without an identifiable cause. The lymphocytosis is usually between 2×10^9 and 20×10^9/L. The malignant T-LGL cells are positive for CD3 and CD8, and CD57/CD16 are expressed in most cases, but CD56 is negative. It may arise de novo or in the context of rheumatoid arthritis or other autoimmune disorder. T-LGL must be distinguished from reactive LGL populations which may be seen in the setting of chronic viral infections or autoimmune conditions. Assessment of clonality with T-cell receptor PCR is often helpful in establishing the diagnosis. Most cases have an indolent clinical course, and T-LGL is usually not considered a life-threatening disease; however, rare cases with an aggressive course have been described. Chronic lymphoproliferative disorder of NK cells (CLPD-NK) has similar clinic features and indolent course, but the neoplastic cells have an NK-cell immunophenotype with expression of CD16 and CD56, variable expression of CD2, CD5, and CD7, and lack of surface CD3. STAT3 mutations are found in about 30% of both T-LGL and CLPD-NK. Of note, T-LGL and CLDP-NK should be distinguished from aggressive NK-cell leukemia, which have a fulminant aggressive course (see Chapter 23). In T-LGL and CLDP-NK, moderate splenomegaly is the most common clinical finding, and lymphadenopathy is rare. Severe neutropenia with or without anemia is common, and pancytopenia may be seen. A variety of autoimmune disorders, including hemolytic anemia, thrombocytopenia, and pure red blood cell aplasia, also may occur. If treatment is required for cytopenias, immunomodulatory agents, such as low-dose methotrexate, cyclophosphamide, and cyclosporine A, are often effective, and corticosteroids can provide a useful adjunct. Responses can take up to 4 months, and longer therapy often is needed to maintain the response. Weekly low-dose oral methotrexate is most commonly used as initial therapy, though oral cyclophosphamide at a dose of 50 to 100 mg by mouth daily has anecdotally appeared to be more effective in anemia-predominant disease. Purine analogs have been used in highly refractory patients. Splenectomy may be useful in selected cases with an accompanying splenomegaly, refractory cytopenias, or autoimmune hemolytic anemia or thrombocytopenia. The anti-CD52 monoclonal antibody alemtuzumab can be used in select cases.

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract

Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract is a clonal proliferation typically involving CD8-positive T cells that infiltrate the lamina propria of multiple sites in the small intestine and colon. Patients typically present with abdominal pain, dyspepsia, diarrhea, and weight loss. Biopsies demonstrate a lymphoid infiltrate in the lamina propria that shows little histologic evidence of epithelial invasion, and, accordingly, patients generally have an indolent relapsing clinical course. Response to chemotherapy is poor, but patients have prolonged survival with persistent disease.

Primary cutaneous acral $CD8^+$ T-cell lymphoma

Primary cutaneous acral $CD8^+$ T-cell lymphoma is a rare cutaneous lymphoma that typically occurs at acral sites, such as the ear, nose, or soles of the feet as an isolated papule or nodule with a history of slow growth. Histologically, there is a dermal proliferation of intermediate-sized atypical $CD8^+$ T cells that lacks aggressive features, such as angiodestruction and necrosis, and spares the epidermis. Local excision or radiotherapy typically leads to complete remission.

Bibliography

Overview of lymphocyte development

Küppers R, Klein U, Hansmann ML, Rajewsky K. Cellular origin of human B-cell lymphomas. *N Engl J Med*. 1999;341(20):1520-1529. *An overview of the biology of lymphocyte development and its relation to lymphomagenesis*.

Kurtz DM, Green MR, Bratman SV, et al. Noninvasive monitoring of diffuse large B-cell lymphoma by immunoglobulin high-throughput sequencing. *Blood*. 2015;125(24):3679-3687.

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908730/chapter_22.pdf by Eleni Gavriilaki on 10 December 2022

Lenz G, Staudt LM. Aggressive lymphomas. *N Engl J Med*. 2010;362(15):1417-1429.

Rossi D, Diop F, Spaccarotella E, et al. Diffuse large B-cell lymphoma genotyping on the liquid biopsy. *Blood*. 2017;129(14):1947-1957.

Swerdlow SH, Campo E, Harris NL, et al, eds. WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Revised 4th ed. IARC Press; 2017.

Lymphoma epidemiology, staging, and evaluation

Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphoma imaging working group. *J Clin Oncol*. 2014;32(27):3048-3058.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32(27):3059-3068.

Morton LM, Slager SL, Cerhan JR, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph NHL Subtypes Project. *J Natl Cancer Inst Monogr*. 2014;48:130-144.

Follicular lymphoma

Advani R, Rosenberg SA, Horning SJ. Stage I and II follicular non-Hodgkin lymphoma: long-term follow-up of no initial therapy. *J Clin Oncol*. 2004;22(8):1454-1459.

Ardeshna KM, Qian W, Smith P, et al. Rituximab versus a watch and wait approach in patients with advanced-stage asymptomatic, non-bulky follicular lymphoma: an open label randomised phase 3 trial. *Lancet Oncol*. 2014;15(4):424-435.

Batlevi CL, Sha F, Alperovich A, et al. Follicular lymphoma in the modern era: survival, treatment outcomes, and identification of high-risk subgroups. *Blood Cancer J*. 2020;10:74.

Campbell BA, Voss N, Woods R, et al. Long-term outcomes for patients with limited stage follicular lymphoma: involved regional radiotherapy versus involved node radiotherapy. *Cancer*. 2010;116(16):3797-3806.

Casulo C, Byrtek M, Dawson KL, et al. Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: an analysis from the National LymphoCare Study. *J Clin Oncol*. 2015;33(23):2516-2522.

Casulo C, Friedberg JW, Ahn KW, et al. Autologous transplantation in follicular lymphoma with early therapy failure: a national LymphoCare study and Center for International Blood and Marrow Transplant Research analysis. *Biol Blood Marrow Transplant*. 2018;24(6):1163-1171.

Conconi A, Lobetti-Bodoni C, Lopez-Guillermo A, et al. Life expectancy of young adults with follicular lymphoma. *Ann Oncol*. 2015;26(11):2317-2322.

Dave SS, Wright G, Tan B, et al. Prediction of survival in follicular lymphoma based on molecular features of tumor-infiltrating immune cells. *N Engl J Med*. 2004;351(21):2159-2169.

Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2017;35(35):3898-3905.

Federico M, Luminari S, Dondi A, et al. R-CVP versus R-CHOP versus R-FM as first line therapy for advanced stage follicular lymphoma: final result of FOLL5 trial conducted by the Fondazione Italiana Linformi. *J Clin Oncol*. 2013;31(12):1506-1513.

Flinn IW, Miller CB, Ardeshna KM, et al. DYNAMO: a Phase II study of duvelisib (IPI-145) in patients with refractory indolent non-Hodgkin lymphoma. *J Clin Oncol*. 2019;37:912-922.

Flinn IW, van der Jagt R, Kahl BS, et al. Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study. *Blood*. 2014;123(19):2944-2952.

Fowler NH, Samaniego F, Jurczak W, et al. Umbralisib, a dual PI3Kδ/CK1ε inhibitor in patients with relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2021;39(15):1609-1618.

Friedberg JW, Byrtek M, Link BK, et al. Effectiveness of first-line management strategies for stage I follicular lymphoma: analysis of the national lymphocare study. *J Clin Oncol*. 2012;30(27):3368-3375.

Friedberg JW, Taylor MD, Cerhan JR, et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. *J Clin Oncol*. 2009;27(8):1202-1208.

Gopal AK, Kahl BS, de Vos S, et al. PI3K inhibition by idelalisib in patients with relapsed indolent lymphoma. *N Engl J Med*. 2014;370(11):1008-1018.

Hiddemann W, Barbui AM, Canales MA, et al. Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the GALLIUM study: influence of chemotherapy on efficacy and safety. *J Clin Oncol*. 2018;36:2395-2404.

Hiddemann W, Kneba M, Dreyling M, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. *Blood*. 2005;106(12):3725-3732.

Kahl BS, Bartlett NL, Leonard JP, et al. Bendamustine is effective therapy in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma: results from a multicenter study. *Cancer*. 2010;116(1):106-114.

Kahl BS, Hong F, Williams ME, et al. Rituximab extended schedule or re-treatment trial for low-tumor burden follicular lymphoma: eastern cooperative oncology group protocol e4402. *J Clin Oncol*. 2014;32(28):3096-3102.

Khouri IF, Saliba RM, Erwin WD, et al. Nonmyeloablative allogeneic transplantation with or without ^{90}yttrium-ibritumomab tiuxetan is potentially curative for relapsed follicular lymphoma: 12-year results. *Blood*. 2012;119(26):6373-6378.

Leonard JP, Jung SH, Johnson J, et al. Randomized trial of lenalidomide alone versus lenalidomide plus rituximab in patients with recurrent follicular lymphoma: CALGB 50401 (Alliance). *J Clin Oncol*. 2015;33(31):3635-3640.

Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2019;37:1188-1199.

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Link BK, Maurer MJ, Nowakowski GS, et al. Rates and outcomes of follicular lymphoma transformation in the immunochemotherapy era: a report from the University of Iowa/MayoClinic Specialized Program of Research Excellence Molecular Epidemiology Resource. *J Clin Oncol*. 2013;31(26):3272-3278.

MacManus M, Fisher R, Roos D, et al. Randomized trial of systemic therapy after involved-field radiotherapy in patients with early-stage follicular lymphoma: TROG 99.03. *J Clin Oncol*. 2018;36(29):2918-2925.

Marcus R, Davies A, Ando K, et al. Obinutuzumab for the first-line treatment of follicular lymphoma. *N Engl J Med*. 2017;377(14):1331-1344.

Marcus R, Imrie K, Solal-Celigny P, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol*. 2008;26(28):4579-4586.

Maurer MJ, Bachy E, Ghesquières H, et al. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. *Am J Hematol*. 2016;91(11):1096-1101.

Morabito F, Baldini L, Stelitano C, et al; Gruppo Italiano per lo studio dei linfomi. Prospective study of indolent non-follicular non-Hodgkin's lymphoma: validation of Gruppo Italiano per lo studio dei linfomi (GISL) prognostic criteria for watch and wait policy. *Leuk Lymphoma*. 2002;43(10):1933-1938.

Morschhauser F, Tilly H, Chaidos A, et al. Tazemetostat for patients with relapsed or refractory follicular lymphoma: an open-label, single-arm, multicentre, phase 2 trial. *Lancet Oncol*. 2020;21(11):1433-1442.

Pugh TJ, Ballonoff A, Newman F, Rabinovitch R. Improved survival in patients with early stage low-grade follicular lymphoma treated with radiation. *Cancer*. 2010;116:3843-3845.

Rezvani AR, Storer B, Maris M, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in relapsed, refractory, and transformed indolent non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26(2):211-217.

Rohatiner AZS, Nadler L, Davies AJ, et al. Myeloablative therapy with autologous bone marrow transplantation for follicular lymphoma at the time of second or subsequent remission: long-term follow- up. *J Clin Oncol*. 2007;25(18):2554-2559.

Rummel MJ, Niederle N, Maschmeyer G, et al. Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial. *Lancet*. 2013;381(9873):1203-1210.

Salles G, Seymour JF, Offner F, et al. Rituximab maintenance for 2 years in patients with high tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): a phase 3, randomised controlled trial. *Lancet*. 2011;377(9759):42-51.

Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol*. 2003;21(21):3918-3927.

Sehn LH, Chua N, Mayer J, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. *Lancet Oncol*. 2016;17(8):1081-1093.

van Besien K, Loberiza FR, Bajorunaite R, et al. Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma. *Blood*. 2003;102(10):3521-3529.

Marginal zone lymphomas

Ferreri AJ, Govi S, Pasini E, et al. Chlamydophila psittaci eradication with doxycycline as first-line targeted therapy for ocular adnexae lymphoma: final results of an international phase II trial. *J Clin Oncol*. 2012;30(24):2988-2994.

Goda JS, Gospodarowicz M, Pintilie M, et al. Long-term outcome in localized extranodal mucosa-associated lymphoid tissue lymphomas treated with radiotherapy. *Cancer*. 2010;116(16):3815-3824.

Hermine O, Lefrère F, Bronowicki JP, et al. Regression of splenic lymphoma with villous lymphocytes after treatment of hepatitis C virus infection. *N Engl J Med*. 2002;347(2):89-94.

Kalpadakis C, Pangalis GA, Angelopoulou MK, et al. Treatment of splenic marginal zone lymphoma with rituximab monotherapy: progress report and comparison with splenectomy. *Oncologist*. 2013;18(2):190-197.

Kuo SH, Yeh KH, Wu MS, et al. Helicobacter pylori eradication therapy is effective in the treatment of early-stage H pylori-positive gastric diffuse large B-cell lymphomas. *Blood*. 2012;119(21):4838-4844.

Leonard JP, Trneny M, Izutsu K, et al; AUGMENT Trial Investigators. AUGMENT: a phase III study of lenalidomide plus rituximab versus placebo plus rituximab in relapsed or refractory indolent lymphoma. *J Clin Oncol*. 2019;37:1188-1199.

Nakamura S, Sugiyama T, Matsumoto T, et al. Long-term clinical outcome of gastric MALT lymphoma after eradication of *Helicobacter pylori*: a multicentre cohort follow-up study of 420 patients in Japan. *Gut*. 2012;61(4):507-513.

Noy A, de Vos S, Thieblemont C, et al. Targeting Bruton tyrosine kinase with ibrutinib in relapsed/refractory marginal zone lymphoma. *Blood*. 2017;129(16):2224-2232.

Thieblemont C, Berger F, Dumontet C, et al. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood*. 2000;95(3):802-806.

Zucca E, Conconi A, Laszlo D, et al. Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 randomized study. *J Clin Oncol*. 2013;31(5):565-572.

Waldenström macroglobulinemia

Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *J Clin Oncol*. 2007;25(22):3344-3349.

Dimopoulos MA, Kastritis E, Owen RG, et al. Treatment recommendations for patients with Waldenström macroglobulinemia

Downloaded from http://ashpublications.org/books/book/chapter-pdf/1908730/chapter_22.pdf by Eleni Gavriilaki on 10 December 2022

(WM) and related disorders: IWWM-7 consensus. *Blood*. 2014; 124(9):1404-1411.

Kyriakou C, Canals C, Cornelissen JJ, et al. Allogeneic stem-cell transplantation in patients with Waldenström macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28(33):4926-4934.

Kyriakou C, Canals C, Sibon D, et al. High-dose therapy and autologous stem-cell transplantation in Waldenstrom macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010; 28(13):2227-2232.

Treon SP, Branagan AR, Hunter Z, Santos D, Tournhilac O, Anderson KC. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenström's macroglobulinemia. *Ann Oncol*. 2004;15(10):1481-1483.

Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenström macroglobulinemia. *Blood*. 2014;123(18):2791-2796.

Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenström macroglobulinemia with bortezomib, dexamethasone, and rituximab: WMCTG clinical trial 05-180. *J Clin Oncol*. 2009;27(23):3830-3835.

Hairy cell leukemia

Chihara D, Arons E, Stetler-Stevenson M, et al. Randomized phase II study of first-line cladribine with concurrent or delayed rituximab in patients with hairy cell leukemia. *J Clin Oncol*. 2020;38(14):1527-1538.

Else M, Dearden CE, Matutes E, et al. Long-term follow-up of 233 patients with hairy cell leukaemia, treated initially with pentostatin or cladribine, at a median of 16 years from diagnosis. *Br J Haematol*. 2009;145(6):733-740.

Grever MR. How I treat hairy cell leukemia. *Blood*. 2010;115(1): 21-28.

Jones G, Parry-Jones N, Wilkins B, Else M, Catovsky D; British Committee for Standards in Haematology. Revised guidelines for the diagnosis and management of hairy cell leukaemia and hairy cell leukaemia variant. *Br J Haematol*. 2012;156(2):186-195.

Kreitman RJ, Dearden C, Zinzani PL, et al. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. *Leukemia*. 2018;32(8):1768-1777.

Park JH, Shukla M, Salcedo JM, et al. First line chemo-free therapy with the BRAF inhibitor vemurafenib combined with obinutuzumab is effective in patients with Hcl [abstract]. *Blood*. 2019;134(suppl 1). Abstract 3998.

Pettirossi V, Santi A, Imperi E, et al. BRAF inhibitors reverse the unique molecular signature and phenotype of hairy cell leukemia and exert potent antileukemic activity. *Blood*. 2015;125(8):1207-1216.

Ravandi F, O'Brien S, Jorgensen J, et al. Phase 2 study of cladribine followed by rituximab in patients with hairy cell leukemia. *Blood*. 2011;118(14):3818-3823.

Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. *N Engl J Med*. 2011;364(24):2305-2315.

Indolent T-cell lymphomas

Bazarbachi A, Suarez F, Fields P, Hermine O. How I treat adult T-cell leukemia/lymphoma. *Blood*. 2011;118(7):1736-1745.

Bekkenk MW, Geelen FA, van Voorst Vader PC, et al. Primary and secondary cutaneous CD30(+) lymphoproliferative disorders: a report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. *Blood*. 2000;95(12):3653-3661.

Johnson L, O'Donoghue JM, McLean N, et al. Breast implant associated anaplastic large cell lymphoma: the UK experience. Recommendations on its management and implications for informed consent. *Eur J Surg Oncol*. 2017;43(8):1393-1401.

Kim YH, Bagot M, Pinter-Brown L, et al; MAVORIC Investigators. Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial. *Lancet Oncol*. 2018;19(9):1192-1204. Erratum in: *Lancet Oncol*. 2018;19(11):e581.

Prince HM, Kim YH, Horwitz SM, et al. Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial. *Lancet*. 2017;390(10094):555-566.

Prince HM, Whittaker S, Hoppe RT. How I treat mycosis fungoides and Sézary syndrome. *Blood*. 2009;114(20):4337-4353.

Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue. 4th ed. IARC Press; 2008.

Vose J, Armitage J, Weisenburger D. International T-cell Lymphoma Project. International peripheral T-cell lymphoma study: pathology findings and clinical outcomes. *J Clin Oncol*. 2008;25:4124-4130.

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